Privilégier les anciennes céphalosporines pour traiter les infections à SASM?

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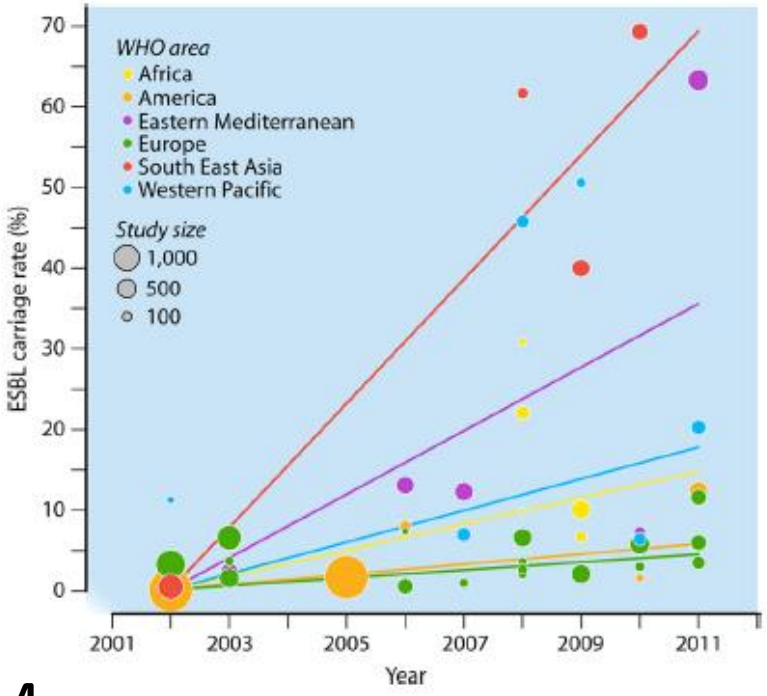
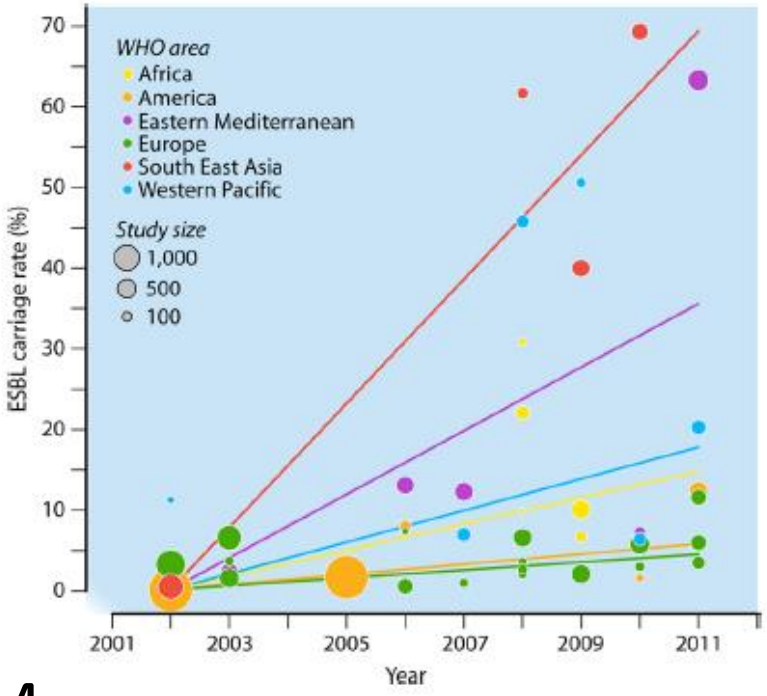
Céphalosporines, céphalosporines…
Entérobactéries R aux C3G, monde



Globalisation de CTX-M

Woerther et al. CMR 2013

Céphalosporines, céphalosporines…
Entérobactéries R aux C3G, AP-HP



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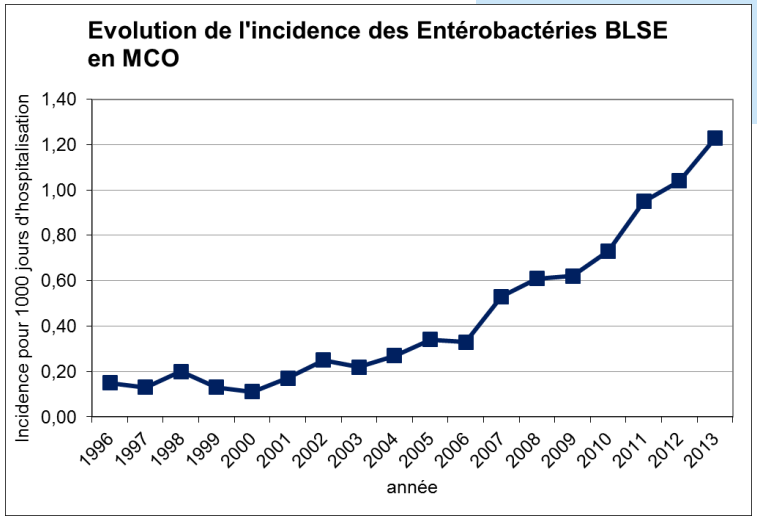
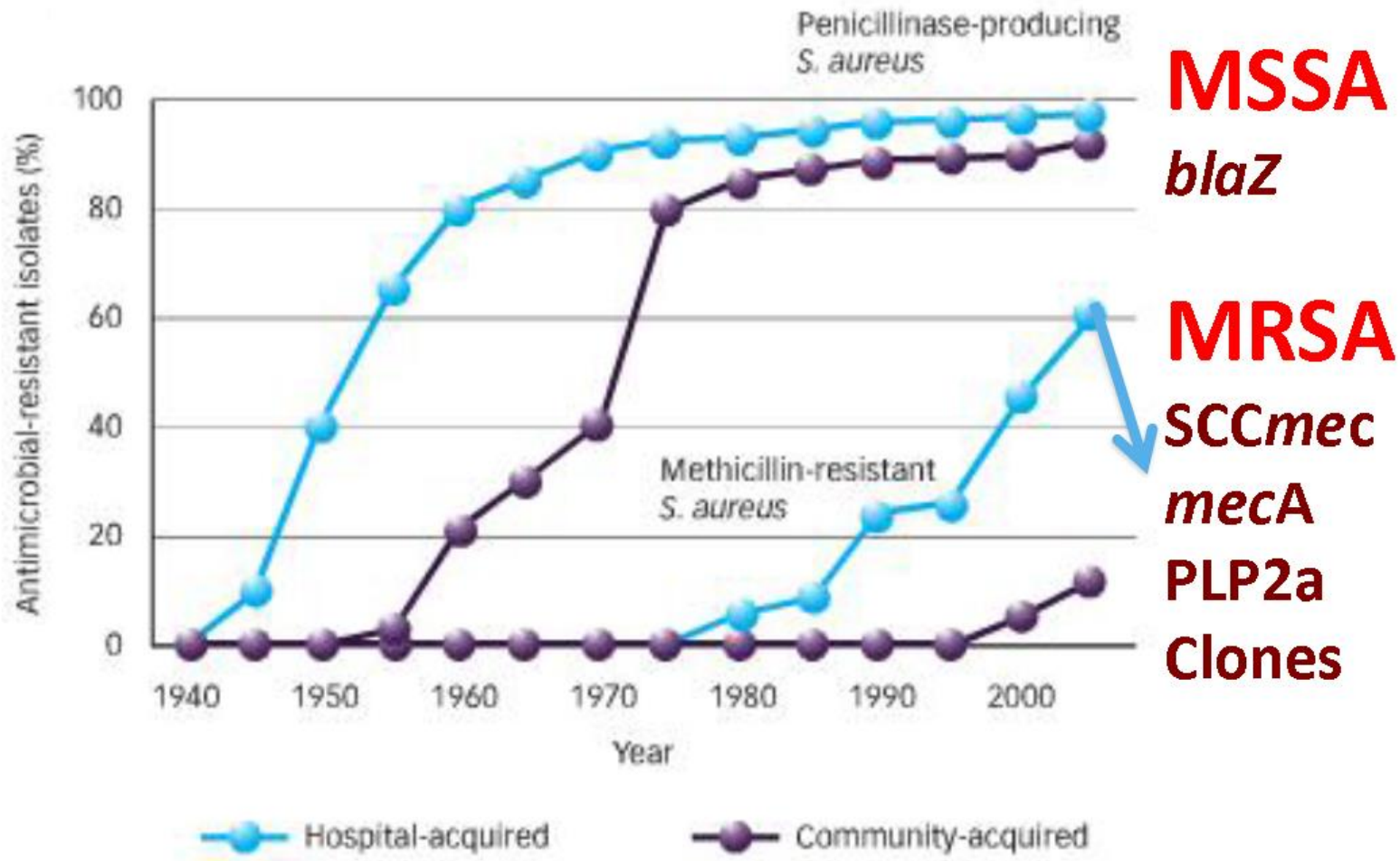


Source : Collégiale Bactériologie-Virologie-Hygiène AP-HP

blaZ et céphalosporines?



Diapositive Tristan Ferry

Quelle est « La » question(s) ?

- Quel est le réel impact écologique des anciennes céphalosporines?
- Quel antibiotique utiliser en cas d'allergie vraie aux pénicillines?
- Quelle est la tolérance réelle des pénicillines à forte dose?
- Comment adapter la posologie des pénicillines en cas d'insuffisance rénale?
- Les anciennes céphalosporines sont-elles aussi efficaces que les péni M?

Quel est l’impact écologique des anciennes céphalosporines?

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Réponse dans les études cliniques?

Cas témoin rétrospective hospitalière, H/F
Bactériémie à EBLSE
N=88 (44 BLSE, 44 non BLSE)

Risk factor	OR (95% CI)	*p*-Value[a]
Known colonization with an ESBL-producing organism	46.2 (3.45–619)	<0.0001
Exposure to first-generation cephalosporins within preceding 12 months	12.3 (1.01–148)	0.049
Exposure to quinolone antibiotics within preceding 12 months	6.56 (1.79–24)	0.0066
Total inpatient days within preceding 12 months	1.033 (1.001–1.066)[b]	0.0017
Days admitted under general surgery within preceding 12 months	0.95 (0.9–0.99)[b]	0.0019

Freeman et al. Internat JID 2012

Cas témoin rétrospective
Base hospitaliere de laboratoire, H/F
Infection à E. coli ou KP R aux C 3G
N=212 (106 BLSE ou AmpC, 106 non R)

	OR	95% CI	P
Prior nursing home stay (previous 6 months)	8.28	1.70, 40.26	0.01
Prior 1st generation cephalosporin use	2.38	1.13, 5.03	0.02
Prior 3rd generation cephalosporin use	4.52	1.44, 14.25	0.01
Length of stay before infection >14 days	3.05	1.44, 6.49	0.004
Prior acute care facility stay (previous 6 months)	1.96	1.06, 3.62	0.03

Ofner-Agostini et al. Can JID Microbiol 2009

Quel est l'impact écologique des anciennes céphalosporines?
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Days adm				0.0019

2 études / plus de 60 publiées (infections urinaires)

Qualité des études?

Freeman et al. Internat JID 2012

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Quel est l'impact écologique des anciennes céphalosporines?
Réponse dans les études animales?

	Molecule	Type of subjects	Number of subjects	Route of administration	Dose mg/day	Treatment duration	Entero-bacteria	Enterococci	Yeasts	Anaerobic cocci	Anaerobic GPB	*Clostridia*	*Bacteroides* spp.	Total anaerobes
First-generation cephalosporins	Cefalexin	V	6	po	250 x 4	4 days	=	ND	ND	ND	ND	ND	ND	ND
	Cefalexin	A/V	9/3 *	po	2000	Variable	=	=	ND	-	-	=	=	=
	Cefradine	V	6	po	1000 x 2	7 days	=	=	ND	ND	+	ND	ND	=
	Cefradoxil	V	10	po	500 x 2	10 days	=	=	ND	ND	ND	=	=	=
	Cefradoxil	C	5	po	30/kg	ND	=	=	ND	ND	--	ND	--	ND
	Cefaloridine	V	6	IV	1000	1 dose	=	=	ND	ND	=	=	=	=
	Cefalotine	C	1	IV	100/kg	6 days	=	=	=	=	=	=	=	ND
	Cefazolin	V	6	IV	1000	1 dose	=	=	ND	ND	=	=	=	=
	Cefazolin	A	7	IV	1000 x 3	4 days	=	=	=	=	-	=	=	=
	Cefazolin	C	18	IV	25/kg	1 dose	ND	ND	ND	ND	-	ND	=	ND
	Cefazolin	V	15	IV	3000 x 2	4 days	-	=	++	ND	-	ND	-	ND

Grall et al. En cours de reviewing

Quel est l'impact écologique des anciennes céphalosporines?

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	Cefradine	V	6	po	1000 x 2	7 days	=	=	ND	ND	+	ND	ND	=
	Cefradoxil	V	10	po	500 x 2	10 days	=	=	ND	ND	ND	=	=	=
	Cefradoxil	C	5	po	30/kg	ND	=	=	ND	ND	--	ND	--	ND
	Cefaloridine	V	6	IV	1000	1 dose	=	=	ND	ND	=	=	=	=
	Cefalotine	C	1	IV	100/kg	6 days	=	=	=	=	=	=	=	ND
	Cefazolin	V	6	IV	1000	1 dose	=	=	ND	ND	=	=	=	=
	Cefazolin	A	7	IV	1000 x 3	4 days	=	=	=	=	-	=	=	=
	Cefazolin	C	18	IV	25/kg	1 dose	ND	ND	ND	ND	-	ND	=	ND
	Cefazolin	V	15	IV	3000 x 2	4 days	-	=	++	ND	-	ND	-	ND
Second-generation cephalosporins	Cefuroxime axetil	V	10	po	250 x 2	7 days	-	+	ND	ND	--	=	=	ND
	Cefuroxime axetil	V	10	po	250 x 2	10 days	=	+	=	ND	=	-	=	ND
	Cefuroxime axetil	A	8	po	250 x 2	10 days	-	=	ND	=	=	=	=	ND
	Cefuroxime axetil	V	10	po	250 x 2	10 days	=	+	=	ND	-	-	=	ND
	Loracarbef	C	6	po	30/kg	ND	=	+	ND	ND	=	ND	=	ND
	Loracarbef	A	40	po	200 x 2	7 days	ND	=	=	ND	ND	ND	ND	=
	Loracarbef	V	20	po	200 x 2	7 days	=	+	ND	=	-	=	=	ND
	Cefbuperazone	A	10	IV	1000 x 2	1 day	--	-	ND	-	--	--	--	ND
	Cefmetazole	C	1	IV	100/kg	10 days	--	=	+	ND	ND	ND	--	ND
	Cefotetan	V	6	IV	2000	1 dose	--	+	ND	ND	=	=	=	=
	Cefotiam	V	15	IV	6000	3 days	-	=	+	ND				
	Cefoxitin	V	6	IV	2000	1 dose	=	=	ND	ND				

Grall et al. En cours de reviewing

Quel antibiotique utiliser en cas d'allergie vraie aux pénicillines?

Vancomycine en cas « d'allergie » aux BL?

MSSAB, cohorte rétrospective bicentrique, n=294, Séoul, Corée, 1998-2006, critère : mortalité

Characteristic	Univariate analysis		Multivariate analysis[a]		Multivariate analysis[b]	
	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Old age (≥65 yr)	1.4 (0.8–2.5)	0.29				
Male gender	1.0 (0.6–1.8)	0.98				
Community-acquired infection	1.2 (0.7–2.2)	0.52				
McCabe classification	7.3 (2.8–19.0)	<0.001	2.7 (0.9–7.7)	0.06	2.7 (0.9–7.7)	0.06
Underlying diseases						
Solid tumor	6.8 (3.6–13.1)	<0.001	4.7 (2.2–9.9)	<0.001	4.8 (2.2–10.3)	<0.001
Hematologic malignancy	0.4 (0.2–1.0)	0.06				
Liver cirrhosis	4.5 (2.4–8.6)	<0.001	3.4 (1.6–7.3)	0.002	3.4 (1.6–7.4)	0.002
Primary sites of infection						
Unknown	3.0 (1.7–5.4)	0.001				
Catheter-related infection	0.1 (0.0–0.4)	0.002				
Pneumonia	2.6 (1.1–6.0)	0.03	2.7 (0.9–7.3)	0.046	2.7 (0.9–7.3)	0.06
Vancomycin treatment	2.8 (1.2–6.4)	0.02	3.4 (1.2–9.3)	0.02	3.3 (1.2–9.5)	0.02

[a] Adjusted for the variables associated with *S. aureus*-related mortality.
[b] Adjusted for the variables associated with *S. aureus*-related mortality and the propensity score of each patient's likelihood of being treated with vancomycin.

KIM SH, Kim KH, KIM HB, Kim NJ, Kim EC et al. AAC 2008

Vancomycine en cas « d'allergie » aux BL?

Cohorte rétrospective, 2003-2010, Vétérans américains
5633 MSSAB, traitement doc 17% vanco, 83% BL
BL = péniM, cefazoline, cefotetan, cefoxitine, cefotaxime,
ceftriaxone, cefepime, ceftaroline, carbapénèmes, et BL + inhibiteurs
Critère : mortalité à 30 jours

B-lactamines vs vancomycine : ORa = 0,65 [0,52-0,80]
PéniM ou Céfazoline vs vancomycine : ORa = 0,57 [0,46-0,71]

McDanell et al. CID 2015

Cohorte rétrospective, 2003-2007, USA, Baltimore, n=267 patients
MSSAB traitées par nafcilline, céfazoline ou vancomycine
38 traités par nafcilline
135 traités par céfazoline
94 traités par vancomycine
Critère : mortalité à 30 jours : 11%

nafcilline ou céfazoline vs vancomycine : ORa = 0,21 [0,09-0,47]

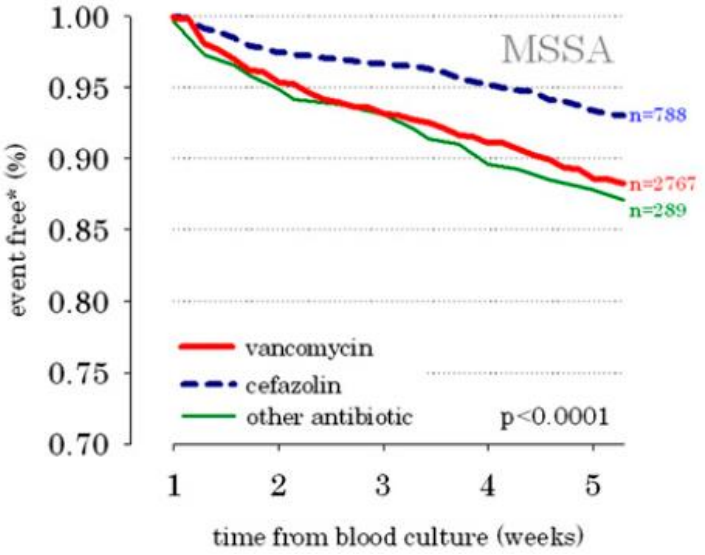
Schweizer et al. BMC ID 2011

Cefazoline chez les hémodialysés chroniques

Prospectif, HD chronique
SAB, n=123, Vanco, n=77, Cefazo, n=46
Grpe vanco : plus jeunes (51 vs 57 ans) et moins de méta secondaires (12% vs 37%)
Critère : décès ou récurrence à S12
vancomycine vs céfazoline (31% vs 13%) : ORa=3,53 [1,15-13,45]

Stryjewski et al. CID 2007

Prospectif, patients HD chroniques, n=293.094
Taux d'incidence des bactériémies : 15,4/100 PA,
Taux d'incidence des bactériémies à SAMS : 2,1/100 PA
56,1% vancomycine, 16,7% céfazoline
Critère : décès ou réadmission J30
Céfazoline vs Vancomycine : HRa=0,62 [0,46-0,84]



Chan KE et al. JASN 2013

Toutes les BL sont elles équivalentes?

Cohorte rétrospective, 1988-2007, Israel
MSSAB traitée par BL, n=498 patients

131 patients traités par péniM ou céfazoline
98 patients traités par cefuroxime
194 patients traités par ceftriaxone ou cefotaxime
61 patients traités par BL + inhibiteur enzymatique

Mortalité à 30 jours, traitement empirique

Variable[b]	OR, 95% CI *n* = 541 patients, deaths = 202	p-value
Empirical antibiotic treatment		
Oxacillin/cefazolin	Reference	
Cefuroxime	1.98 (0.98–4.01)	0.058
Ceftriaxone/cefotaxime	2.24 (1.23–4.08)	0.008
Beta-lactam-beta-lactamase	2.68 (1.23–5.85)	0.013
Other beta-lactams	0.81 (0.35–1.9)	0.629
Age (per 1 year increment)	1.04 (1.02–1.06)	<0.001
Female sex	1.69 (1.08–2.63)	0.021
Poor functional capacity (bedridden)	1.73 (1.02–2.93)	0.041
Malignancy	1.89 (1.15–3.09)	0.012
Shock at onset	5.61 (2.75–11.45)	<0.001
Urea (per 1 mg/dL increment)	1.01 (1.007–1.016)	<0.001
Albumin (per 1 mg/dL increment)	0.54 (0.38–0.78)	0.001
Thrombocytes (per 1 K/μL increment)	0.996 (0.994–0.998)	<0.001
Mechanical ventilation	Not retained in final model	0.078
Skin/soft tissue source of infection		0.111

Paul et al. CMI 2011

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Céfazoline, n=72
Cloxacilline, n=281

Traitement documenté : ORa =0,91 [0,47-1,77]
Traitement probabiliste : ORa=0,81 [0,18-3,6]

Mortalité à 30 jours, traitement empirique

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Paul et al. CMI 2011

Quelle est la tolérance réelle des pénicillines à forte dose?

Tolérance globale de la pénicilline M versus céphalosporines ?

Cohorte rétrospective

Infections SASM

366 patients traités par nafcilline, 119 traités par céfazoline

Arrêt de traitement prématuré : nafcilline vs céfazoline HR=2,81 [1,26-3,68]

9 ATP / nafcilline switché par céfazoline

Event	Nafcillin (n = 366)	Cefazolin (n = 119)	*P* Value
PAD	124 (33.8)	8 (6.7)	<.001
DEEs[a]	114 (31.1)	14 (11.7)	<.001
Rash	51 (13.9)	5 (4.2)	.002
Renal impairment	42 (11.4)	4 (3.3)	.006
Liver abnormalities	30 (8.1)	2 (1.6)	.01
Neutropenia	31 (8.4)	4 (3.3)	.06
Clostridium difficile colitis	9 (2.4)	1 (0.8)	.46

Data are presented as No. (%).

Abbreviations: DEEs, drug-emergent events; PAD, premature antimicrobial discontinuation.

Taux d'incidence d'EIG / 1000 PJ

Type of Therapy	Nafcillin, Rate (95% CI)	Cefazolin, Rate (95% CI)
Monotherapy	16.8 (10.2–27.3)	4.1 (.8–9.8)
As part of polytherapy	17.4 (10.2–27.6)	5.0 (1.6–12.0)
All patients	16.9 (10.4–27.3)	4.8 (1.1–10.2)

Youngster et al. CID 2014

Tolérance globale de la pénicilline M forte dose versus céphalosporines ?

Cohorte rétrospective 2008-2012, 93 bactériémie à SASM, 100% B compliquées (EI, ostéo-arthrites)
93 patients; 59 patients / céfazoline (6g/j), 34 patients / oxacilline (12g/j)

Outcome or parameter	Overall ($n = 93$)	Oxacillin ($n = 34$)	Cefazolin ($n = 59$)	P value
All adverse drug events	12 (13)	10 (30)	2 (3)	0.0006
Rash	2 (2)	1 (3)	1 (2)	1.0
Elevated transaminases	6 (6)	6 (18)	0 (0)	0.002
Elevated serum creatinine	1 (1)	1 (3)	0 (0)	0.37
Leukopenia	1 (1)	1 (3)	0 (0)	1.0
Diarrhea	1 (1)	0 (0)	1 (2)	0.37
Other	1 (1)	1 (3)	0 (0)	0.37
Discontinued due to adverse drug event	9 (10)	7 (21)	2 (3)	0.01

Li et al. AAC 2014

Tolérance rénale de la pénicilline M à forte dose?

Cohorte prospective
Faisant suite aux changements de recommandations d'ATBP dans la chirurgie orthopédique
N=198, Céfuroxime, n=48 puis n=52, forte dose péniM (5-8g)+genta, n=52, faible dose péniM (3-4g)+genta n=46,
Critère = insuffisance rénale aigue
3 patients en HD temporaire, 2 PBR néphrite tubulo-intersticielles
Aucune infection à C. difficile
Arrêt de traitement prématuré : nafcilline vs céfazoline HR=2,81 [1,26-3,68]
9 ATP / nafcilline switché par céfazoline

	Univariate model	Multivariate model
Prophylactic cefuroxime 1	1.00	1.00
Prophylactic HD flucloxacillin with single-dose gentamicin	11.88 (3.73–37.86)	14.53 (4.25–49.71)
Prophylactic LD flucloxacillin with single-dose gentamicin	3.06 (0.88–10.56)	2.96 (0.81–10.81)
Prophylactic cefuroxime 2	1.71 (0.47–6.26)	2.01 (0.52–7.73)
Male versus female	2.88 (1.47–5.62)	3.26 (1.50–7.08)
ACEI/ARB versus none	2.89 (1.46–5.72)	3.07 (1.40–6.74)

Challagundla et al. NDT 2012

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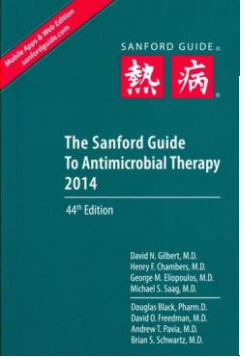
Challagundla et al. NDT 2012

Comment adapter la posologie des pénicillines en cas d'insuffisance rénale?



Comment adapter la posologie des pénicillines en cas d'insuffisance rénale?

Oxacilline

No data

Cefazoline

Clairance de la créatinine	Dose de charge	Dose d'entretien
50 à 20 ml/mn	500 mg	250 mg par jour toutes les 6 h ou 500 mg toutes les 12 h
20 à 10 ml/mn	500 mg	250 mg toutes les 12 h ou 500 mg toutes les 24 h
10 à 5 ml/mn	500 mg	250 mg toutes les 24-36 h ou 500 mg toutes les 48-72 h
< 5 ml/mn sujets hémodialysés	500 mg voie I.V.	500 mg toute les 72 heures

Les céphalosporines de 1ère génération sont-elles aussi efficaces que les pénicillines M?

L’effet inoculum des β-lactamases

Modèle de lapin, 2 souche de SASM, +/- β-lactamases

Strain of *S. aureus*, bacteria/ml	Cefoxitin		Cefazolin	
	MIC	MBC	MIC	MBC
β-Lactamase–positive				
5×10^7	3.2	200	125	500
5×10^5	3.2	3.2	1	250
5×10^3	3.2	3.2	0.25	0.5
β-Lactamase–negative				
5×10^7	3.2	200	1	250
5×10^5	3.2	3.2	0.5	0.5
5×10^3	3.2	3.2	0.25	0.25

Goldman et al. JID 1980

Seuils des concentrations critiques pour la céfazoline : S ≤ 8 mg/l et R > 32 mg/l

L'effet inoculum des β-lactamases

Modèle de lapin, 2 souche de SASM, +/- β-lactamases

Strain of *S. aureus*, bacteria/ml	Cefoxitin MIC	Cefoxitin MBC	Cefazolin MIC	Cefazolin MBC
β-Lactamase–positive				
5×10^7	3.2	200	125	500
5×10^5	3.2	3.2	1	250
5×10^3	3.2	3.2	0.25	0.5
β-Lactamase–negative				
5×10^7	3.2	200	1	250
5×10^5	3.2	3.2	0.5	0.5
5×10^3	3.2	3.2	0.25	0.25

Goldman et al. JID 1980

185 BSASM, données humaines

blaZ gene type (*n*) and parameter	Cefazolin MIC (µg/ml): Standard inoculum[b]	Cefazolin MIC (µg/ml): High inoculum[c]	No. (%) of strains exhibiting inoculum effect: ≥4-fold increase[d]	No. (%) of strains exhibiting inoculum effect: ≥4-fold increase to nonsusceptible MIC[e]
Type A (48)				
Mean (GM)[a]	1.2 (1.1)	7.6 (3.7)	22 (46)	8 (17)
MIC_{50}	1	4		
Type B (43)				
Mean (GM)	1.2 (1.1)	2.1 (1.9)	3 (7)	0
MIC_{50}	1	2		
Type C (49)				
Mean (GM)	1.1 (1.0)	3.2 (2.8)	22 (45)	0
MIC_{50}	1	4		
Type D (2)				
Mean (GM)	1.0 (1.0)	2.0 (2.0)	0	0
MIC_{50}	1	2		
blaZ negative (43)				
Mean (GM)	0.8 (0.77)	1.4 (1.2)	3 (7)	0
MIC_{50}	1	1		

Seuils des concentrations critiques pour la céfazoline : S ≤ 8 mg/l et R > 32 mg/l

Livorsi et al. AAC 2012

La prévalence des β-lactamases chez SASM

185 BSASM, multicentrique, Atlanta (Georgia), 2010

142/185 SASM blaZ+ : 77% (26% type A, 23% type B, 26% type C, 1% type D)

50/185 (27%) CMI x4 ou plus, 8 (4%) CMI>32 (R)

Livorsi et al. AAC 2012

98 souches de SASM, multicentrique, Argentine-USA

85/98 SASM blaZ+ : 77% (26% type A, 15% type B, 46% type C)

19/98 montrant un effet inoculum : 9 A type, 10 C type

Nonnini et al. AAC 2012

220 BSASM, monocentrique, Seoul (South Korea), 2008-2011

198/220 (90%) SASM *blaZ+ (*17% type A, 20% type B, 53% type C, 1% type D)

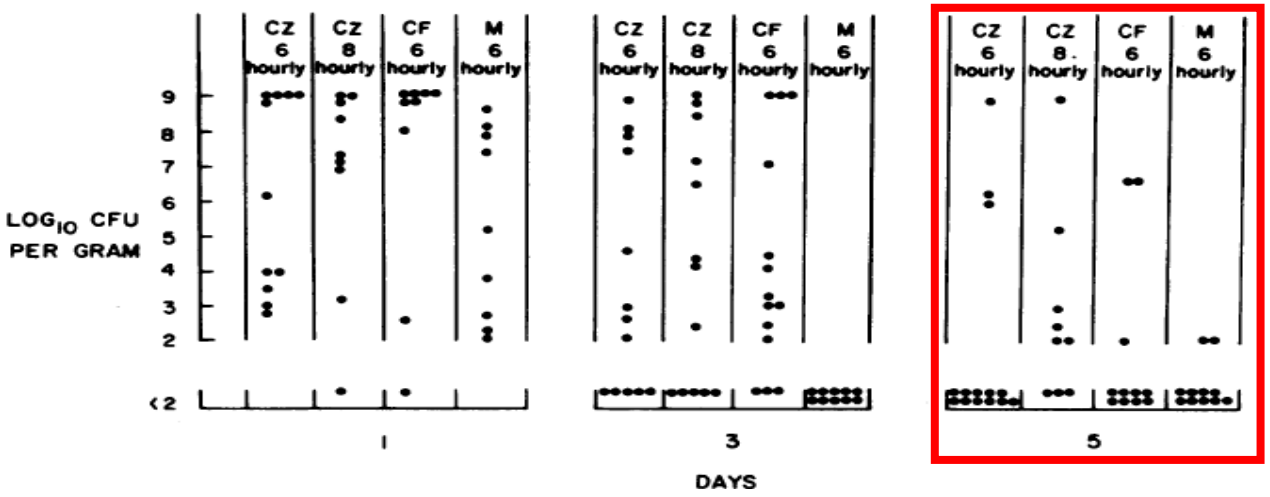
Chong et al. EJCMID 2014

L'impact des β-lactamases du SASM dans le modèle animal?

Modèle animal d'endocardite

Comparaison de la méthicilline, céphalotine et céfazoline

1 souche de SASM producteur de β-lactamase A

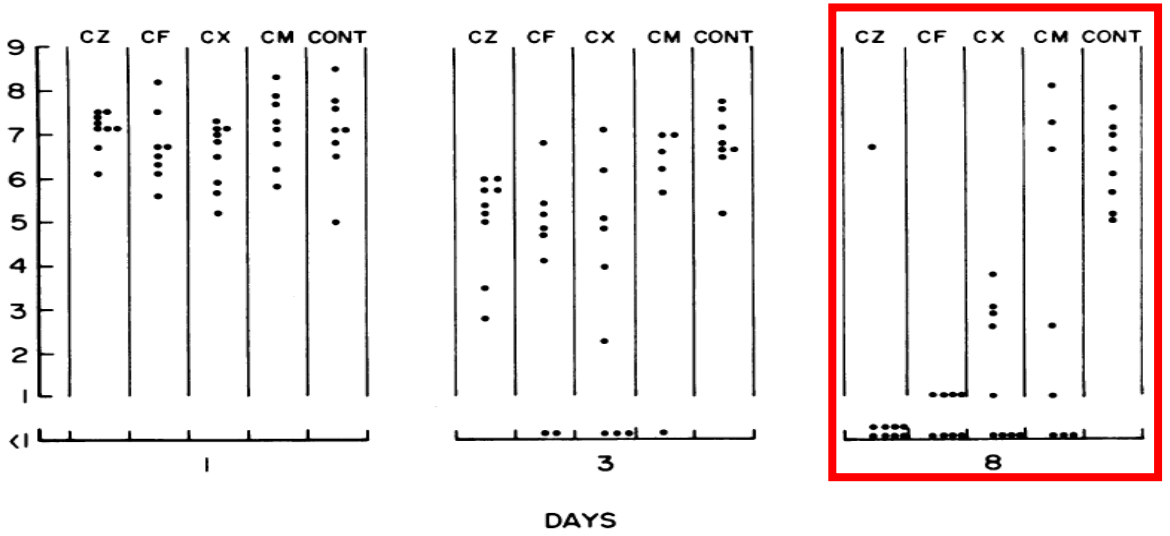


Carrizosa et al. AAC 1977

Modèle animal d'abcès profond

Comparaison de céfazoline, céphalotine, céfoxitine et céfamandole

1 souche de SASM producteur de β-lactamase A



Kaye et al. AAC 1979

L'impact des β-lactamases du SASM dans les études cliniques chez l'homme?

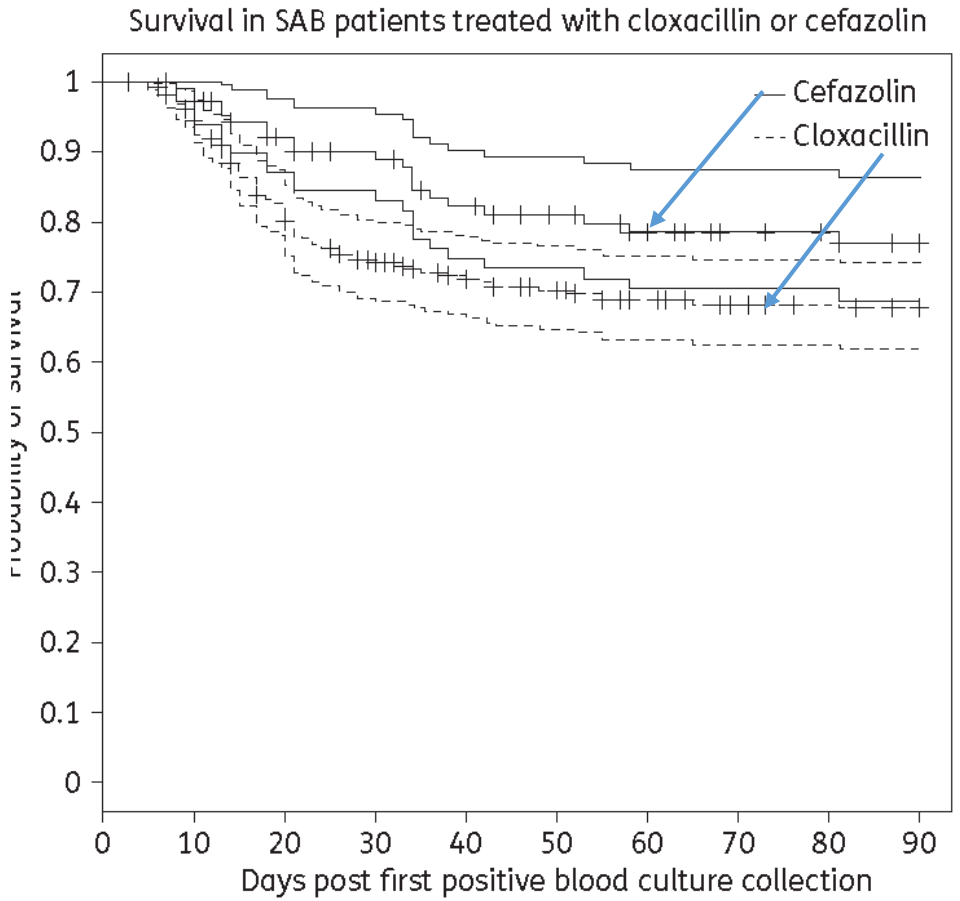
Rétrospective
Etude cas contrôle
Corée du sud
2004-2009
Bactériémie à SASM
26% % B compliquée
Cefazoline n=49
Nafcilline n=84

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	aOR (95% CI)	*P*
Treatment failure at 4 wk				
Male	2.6 (0.8–8.3)	0.11	2.9 (0.8–10.8)	0.12
Cardiovascular disease	5.5 (1.8–17.1)	0.01		
Site of infection				
Catheter related	0.2 (0.0–1.6)	0.12		
Pneumonia	4.4 (1.3–15.2)	0.03	6.0 (1.5–23.7)	0.02
Endocarditis	7.4 (2.2–25.1)	<0.01	8.6 (2.0–36.8)	<0.01
Surgical site	2.5 (0.6–10.5)	0.18		
Primary bacteremia	0.2 (0.0–1.3)	0.07	0.2 (0.0–1.8)	0.15
Eradicated foci of infection	0.3 (0.1–1.5)	0.16		
Metastatic infection	3.6 (0.1–10.3)	0.03		
Cefazolin treatment	0.7 (0.2–2.1)	0.50	1.2 (0.3–4.5)	0.76
Treatment failure at 12 wk				
Old age (≥65 yr)	2.1 (0.8–5.4)	0.14		
Male	2.6 (0.9–7.5)	0.08	3.0 (0.9–10.4)	0.08
Hematologic malignancy	0.3 (0.1–1.2)	0.07	0.2 (0.0–1.2)	0.08
Cardiovascular disease	5.1 (1.8–14.9)	<0.01		
Site of infection				
Catheter related	0.2 (0.0–1.2)	0.08	0.2 (0.0–1.5)	0.11
Pneumonia	4.6 (1.4–14.7)	0.02	5.6 (1.4–21.7)	0.01
Endocarditis	7.5 (2.3–24.5)	<0.01	6.7 (1.6–27.9)	0.01
Primary bacteremia	0.1 (0.0–1.0)	0.02	0.1 (0.0–0.9)	0.04
Eradicated foci of infection	0.2 (0.1–1.1)	0.05		
Metastatic infection	3.1 (1.1–8.2)	0.05		
Cefazolin treatment	0.8 (0.3–2.2)	0.72	1.6 (0.5–5.4)	0.45

Lee et al. AAC 2011

L'impact des β-lactamases du SASM dans les études cliniques chez l'homme?

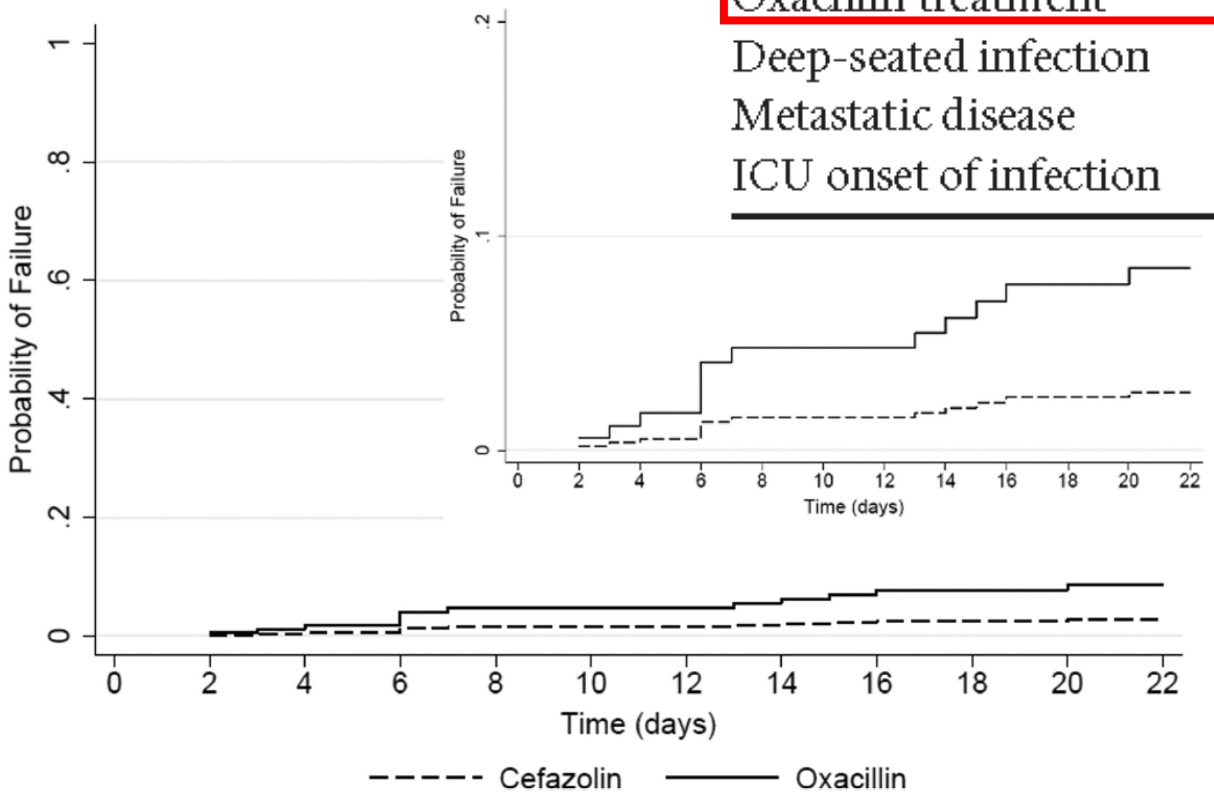
Cohorte rétrospective 2007-2010
Bactériémie à SASM
27% B compliquées
354 pts;
105 patients / céfazoline
246 patients / cloxacilline
27% mortalité à 90 jours :
20% céfazoline vs 30% cloxacilline
HRa = 0,6 [0,36-1,01]



Bai et al. JAC 2015

L'impact des β-lactamases du SASM dans les études cliniques chez l'homme?

Predictor of treatment failure	Multivariate analysis OR (95% CI)	*P* value
Oxacillin treatment	3.76 (0.98–14.4)	0.053
Deep-seated infection	4.52 (1.23–16.6)	0.023
Metastatic disease	4.21 (1.13–15.7)	0.033
ICU onset of infection	4.80 (1.26–18.4)	0.022



Cohorte rétrospective, 2010-2013, Chicago
Bactériémie à SASM, 32% compliquées
161 patients;
103 patients / céfazoline
58 patients / oxacilline

Rao et al. AAC 2015

L'impact des β-lactamases du SASM dans les études cliniques chez l'homme dans les bactériémies compliquées?

Cohorte rétrospective 2008-2012, 93 bactériémie à SASM, 100% B compliquées (EI, ostéo-arthrites)
93 patients; 59 patients / céfazoline (6g/j), 34 patients / oxacilline (12g/j)

Outcome or parameter	Overall ($n = 93$)	Oxacillin ($n = 34$)	Cefazolin ($n = 59$)	P value
Clinical cure at end of therapy	86 (92)	32 (88)	56 (95)	0.25
Duration of bacteremia (days)[b]	4 (2–6)	4 (3–7)	4 (2–5)	0.20
Time to defervescence (days)[b]	2 (1–3)	2 (1–3)	2 (1–4)	0.33
Median no. of blood cultures drawn[b]	4 (4–8)	5 (4–9)	4 (3–8)	0.21
Median no. of blood cultures positive[b]	4 (3–7)	4 (3–10)	4 (2–6)	0.28
Overall treatment failure	30 (32)	16 (47)	14 (24)	0.04
Persistent bacteremia	13/30 (43)	7/16 (44)	6/14 (43)	0.55
Progression of infection on therapy	9/30 (30)	5/16 (31)	4/14 (29)	0.16
Relapse of infection	7/30 (23)	3/16 (19)	4/14 (29)	1.0
Death	1/30 (3)	1/16 (6)	0/14 (0)	0.37
Antibiotic discontinuation due to failure	1 (1)	0 (0)	1 (2)	0.30
Infection-related 90-day readmission	13 (14)	8 (24)	5 (9)	0.06
Recurrence of bacteremia	3 (3)	2 (6)	1 (2)	0.55
30-day mortality	1 (1)	1 (3)	0 (0)	0.37
90-day mortality	1 (1)	1 (3)	0 (0)	0.37

Li et al. AAC 2014

L'impact des β-lactamases du SASM dans les recommandations?

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Native valves						
Methicillin-susceptible staphylococci						
Penicillin-allergic patients[h] or methicillin-resistant staphylococci						
Vancomycin[b] **	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	6,8, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[g] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy**: Daptomycin[c,d]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[g] 10 mg/kg/day i.v. once daily					
Alternative therapy* Cotrimoxazole[a]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		*for *Stahylococcus aureus*
with Clindamycin	1800mg/day IV in 3 doses	1	IIb	C		

Habib et al. European Heart J 2015

2015 ESC Guidelines for the management of infective endocarditis

Table 17 Antibiotic treatment of infective endocarditis due to *Staphylococcus* spp.

Antibiotic	Dosage and route	Duration (weeks)	Class[i]	Level[j]	Ref.[k]	Comments
Prosthetic valves						
Methicillin-susceptible staphylococci						
Penicillin-allergic patients[h] and methicillin-resistant staphylococci						
Vancomycin[b] with	30–60 mg/kg/day i.v. in 2–3 doses	≥ 6	I	B	6,8, 135, 136	**Cephalosporins** cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis. Starting rifampin 3–5 days later than vancomycin and gentamicin has been suggested by some experts. Gentamicin can be given in a single daily dose in order to reduce renal toxicity
Rifampin[e] and	900–1200 mg i.v. or orally in 2 or 3 divided doses	≥ 6	I	B		
Gentamicin[f]	3 mg/kg/day i.v. or i.m. in 1 or 2 doses	2	I	B		
	Paediatric dosing:[g] As above					

Habib et al. European Heart J 2015

2015 ESC Guidelines for the management of infective endocarditis

Antibiotic	Dosage and route	Class[b]	Level[c]
Community-acquired native valves or late prosthetic valves			
Ampicillin with (Flu)cloxacillin *or* oxacillin with Gentamicin[d]	12 g/day i.v. in 4–6 doses 12 g/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIa	C
Vancomycin[d] with Gentamicin[d]	30–60 mg/kg/day i.v. in 2–3 doses 3 mg/kg/day i.v. or i.m. in 1 dose	IIb	C

7.12 Empirical therapy

Treatment of IE should be started promptly. Three sets of blood cultures should be drawn at 30-min intervals before initiation of antibiotics.[202] The initial choice of empirical treatment depends on several considerations:

(1) Whether the patient has received previous antibiotic therapy.
(2) Whether the infection affects a native valve or a prosthesis [and if so, when surgery was performed (early vs. late PVE)].
(3) The place of the infection (community, nosocomial, or non-nosocomial healthcare-associated IE) and knowledge of the local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens (*Table 19*).
(4) Cloxacillin/cefazolin administration is associated with lower mortality rates than other beta-lactams, including amoxicillin/clavulanic acid or ampicillin/sulbactam,[203] and vancomycin for empirically treating MSSA bacteraemia/endocarditis.[159]

Habib et al. European Heart J 2015

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Table 10. Therapy for NVE Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 4–6 equally divided doses	6	*Class I; Level of Evidence C*	For complicated right-sided IE and for left-sided IE; for uncomplicated right-sided IE, 2 wk (see text).
For penicillin-allergic (nonanaphylactoid type) patients				Consider skin testing for oxacillin-susceptible staphylococci and questionable history of immediate-type hypersensitivity to penicillin.
Cefazolin*	6 g/24 h IV in 3 equally divided doses	6	*Class I; Level of Evidence B*	Cephalosporins should be avoided in patients with anaphylactoid-type hypersensitivity to β-lactams; vancomycin should be used in these cases.

Baddour et al. Circulation 2015

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Table 11. Therapy for Endocarditis Involving a Prosthetic Valve or Other Prosthetic Material Caused by Staphylococci

Regimen	Dose* and Route	Duration, wk	Strength of Recommendation	Comments
Oxacillin-susceptible strains				
Nafcillin or oxacillin	12 g/24 h IV in 6 equally divided doses	≥6	*Class I; Level of Evidence B*	Vancomycin should be used in patients with immediate-type hypersensitivity reactions to β-lactam antibiotics (see Table 5 for dosing guidelines); cefazolin may be substituted for nafcillin or oxacillin in patients with non–immediate-type hypersensitivity reactions to penicillins.
Plus				
Rifampin	900 mg per 24 h IV or orally in 3 equally divided doses	≥6		
Plus				
Gentamicin†	3 mg/kg per 24 h IV or IM in 2 or 3 equally divided doses	2		

Baddour et al. Circulation 2015

Conclusions

- L'impact écologique des céphalosporines de 1ère génération sur le microbiote intestinal est faible.
- Ne pas trop vite cataloguer un patient allergique aux pénicillines et essayer de reprendre des β-lactamines.
- Toutes les β-lactamines hors pénicillines ne sont pas équivalentes sur SASM.
- La toxicité des pénicillines à forte dose n'est pas exceptionnelle.
- Le maniement des céphalosporines en cas d'insuffisance rénale est plus aisé que celui des pénicillines.
- L'effet inoculum lié aux β-lactamases (++A) n'a pas d'impact sur la prise en charge des infections non sévères à SASM, bactériémies comprises.
- L'effet inoculum pourrait avoir un impact péjoratif sur la prise en charge des infections compliquées à SASM mais n'est pas démontré aujourd'hui.

L'allergie aux pénicillines étant croisée avec celle aux céphalosporines dans 5 à 10 % des cas
Les concentrations critiques séparent les souches sensibles des souches de sensibilité intermédiaire et ces dernières, des résistantes : S ≤ 8 mg/l et R > 32 mg/l
La céfazoline est éliminée sous forme active, essentiellement par l'urine et, très accessoirement, par la bile.
Après administration IM de 500 mg, on retrouve dans les urines de 6 heures entre 56 et 89% de la dose administrée; ces chiffres sont de 80 à presque 100% au bout de 24 heures.
Biodisponibilité des C1G : cefadroxil oracefal® 90% (poudre ou gel de 500 mg) - cefatrizine cefaperos® 50%
Demi vie 2 heures (vs 30-60 mn/péniM)