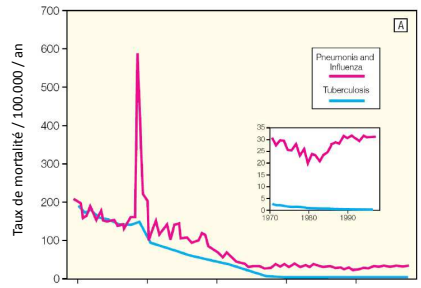
Impact de la résistance sur le devenir des patients

P Chavanet
Annecy 2015



Armstrong GL et al. Trends in infectious disease mortality in the United States during the 20th century. JAMA. 1999;281:61-6.

2

Décès en France infection 2%

Institut national de la statistique et des études économiques
Insee Mesurer pour comprendre

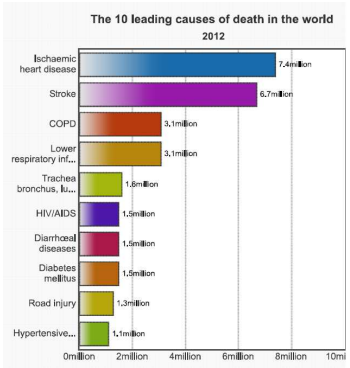
Principales causes de décès en 2012

Principales causes de décès en 2012

en milliers

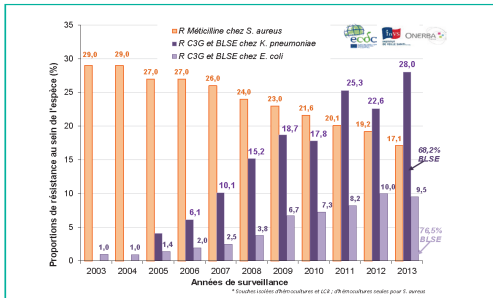
	2012					
	Hommes		Femmes		Ensemble	
	Effectif	en %	Effectif	en %	Effectif	en %
Maladies infectieuses et parasitaires (1)	5,5	2,0	6,0	2,2	11,5	2,1
Tumeurs	92,4	32,9	67,9	24,5	160,3	28,7
dont :						
tumeurs du larynx, trachée, bronches et poumon	*23,3*	*8,3*	*8,3*	*3,0*	*31,6*	*5,7*
tumeurs du côlon	*6,6*	*2,3*	*6,1*	*2,2*	*12,7*	*2,3*
tumeurs du rectum et de l'anus	*2,4*	*0,9*	*2,0*	*0,7*	*4,5*	*0,8*
tumeurs du sein	*0,1*	*0,0*	*11,8*	*4,2*	*11,7*	*2,1*
Troubles mentaux et du comportement	8,9	3,2	12,7	4,6	21,6	3,9
Maladie de l'appareil circulatoire	65,2	23,2	75,8	27,3	141,0	25,3
dont :						
maladies cérébrovasculaires	*20,0*	*7,1*	*14,6*	*5,3*	*34,6*	*6,2*
cardiopathies ischémiques	*13,3*	*4,7*	*18,9*	*6,8*	*32,2*	*5,8*
Maladies de l'appareil respiratoire	19,2	6,8	18,8	6,8	38,0	6,8
Maladies de l'appareil digestif	12,2	4,3	10,4	3,7	22,6	4,1
Causes externes	22,0	7,8	14,8	5,3	36,8	6,6
dont :						
accidents de transport	*2,6*	*0,9*	*0,9*	*0,3*	*3,4*	*0,6*
suicides	*7,3*	*2,6*	*2,4*	*0,9*	*9,7*	*1,7*
Autres causes	55,4	19,7	71,1	25,6	126,5	22,7
Total	**280,7**	**100,0**	**277,6**	**100,0**	**558,3**	**100,0**

Les décès dans le monde

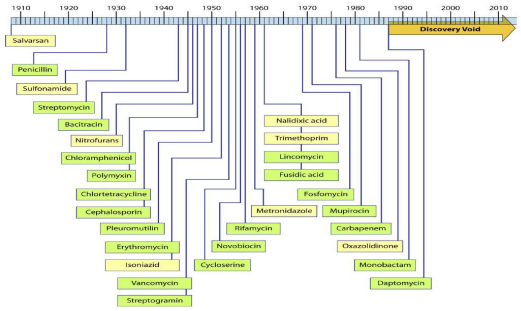


Les résistance france

Évolution de la résistance à la méticilline chez *S. aureus*, et aux céphalosporines de 3e génération chez *K. pneumoniae* et *E. coli*, France, 2002-2013, données EARS-Net France – InVS



Les nouveaux antibiotiques ??



Lynn L. Silver
Challenges of Antibacterial Discovery
CLINICAL MICROBIOLOGY REVIEWS, Jan. 2011, p. 71–109 Vol. 24, No. 1

OMS 2014

Bacterium	Resistance/ decreased susceptibility to:
Escherichia coli	3rd generation cephalosporins, fluoroquinolones
Klebsiella pneumoniae	3rd generation cephalosporins, carbapenems
Staphylococcus aureus	Methicillin (beta-lactam antibiotics) i.e. MRSA
Streptococcus pneumoniae	Penicillin
Nontyphoidal *Salmonella* (NTS)	Fluoroquinolones
Shigella species	Fluoroquinolones
Neisseria gonorrhoeae	3rd generation cephalosporins

OMS 2014
impact de la résistance

	Escherichia coli		*Klebsiella pneumoniae*		*Staphylococcus aureus*
Antibacterial resistance					
	3rd generation cephalosporins	Fluoroquinolones	3rd generation cephalosporins	Carbapenems	MRSA
Outcome parameter					
Bacterium-attributable mortality	Yes (n=4)	No (n=1)	Yes (n=4)	No (n=1)	Yes (n=46)
30-day mortality	Yes (n=11)	Yes (n=5)	Yes (n=7)	Yes (n=3)	Yes (n=16)
Hospital LOS	No (n=3)	No (n=3)	No (n=9)	Unclear (n=3)[a]	Yes (n=50)
Admission to ICU	No (n=1)	Yes (n=1)	Yes (n=3)	ND	No (n=17)
Post-infection LOS	No (n=3)	ND	Yes (n=4)	No (n=1)	Yes (n=27)

Mais aussi

Summaries of surveillance and current resistance situation:

Disease-specific programs
- Tuberculosis
- Malaria
- HIV
- Influenza

Other related areas
- ABR in food-producing animals and food chain
- Antifungal resistance

WHO tools facilitating surveillance of ABR

La résistance est:
- un marqueur de morbidité
- une entrave à un traitement correct
- associée à une surmortalité

Clinical features, antibiotic treatment and outcome of patients with MDRGNB bacteraemia compared with the susceptible control group

Characteristic	MDRGNB, *N*=51, *n* (%)	Non-MDRGNB, *N*=312, *n* (%)	*P*
Inadequate initial empirical antibiotic therapy[c]	35 (69)	29 (9)	<0.001
Time to adequate antibiotic therapy >48 h	21 (41)	13 (4)	<0.001
ICU admission	7 (14)	14 (4)	0.023
Invasive mechanical ventilation	7 (14)	10 (3)	0.005
Early case-fatality rate (7 days)	9 (18)	33 (11)	0.15
Overall case-fatality rate (30 days)	20 (39)	62 (20)	0.003

Gudiol J et al
Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes
J Antimicrob Chemother 2011; 66: 657–663

La résistance est:
- un marqueur de morbidité
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Table 4. Risk factors for overall mortality by univariate and multivariate analysis

Risk factor	Survived, *N*=267, *n* (%)	Died, *N*=82, *n* (%)	*P*	Adjusted OR (95% CI)	*P*
Male sex	164 (61)	55 (67)	0.43	1.06 (0.56–2.00)	0.84
Age in years, median (range)	61 (14–89)	66 (23–89)	0.043	1.02 (0.99–1.05)	0.062
Solid tumour	115 (43)	56 (68)	<0.001	5.04 (2.49–10.19)	<0.001
Graft-versus-host disease	4 (1.5)	5 (6)	0.036	5.40 (0.82–35.39)	0.079
Other co-morbidities	94 (35)	39 (48)	0.051	0.92 (0.48–1.74)	0.80
Polymicrobial bacteraemia	29 (11)	15 (18)	0.087	–	–
Concomitant infection	10 (4)	7 (8.5)	0.085	–	–
Current corticosteroid therapy	85 (32)	55 (67)	<0.001	4.38 (2.39–8.05)	<0.001
Statin use	30 (11)	6 (7)	0.40		
Inadequate empirical antibiotic therapy	39 (15)	20 (24)	0.044	1.57 (0.50–4.90)	0.43
Time to adequate antibiotic therapy >48 h	16 (6)	14 (17)	0.003	2.36 (0.62–8.93)	0.20
Shock at presentation	23 (9)	20 (24)	<0.001	1.57 (0.68–3.61)	0.28
ICU admission	7 (3)	14 (17)	<0.001	11.40 (3.19–40.74)	<0.001
invasive mechanical ventilation	3 (1)	14 (17)	<0.001		
MDRGNB	29 (11)	20 (24)	0.003	3.52 (1.36–9.09)	0.009

Gudiol J et al
Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes
J Antimicrob Chemother 2011; 66: 657–663

Predictors of Carbapenem-Resistant *Klebsiella pneumoniae* Acquisition

TABLE 6. Multivariable risk factors for mortality

Covariate	Patients with CRKP vs patients with CSKS		Patients with CRKP vs hospitalized controls	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Carbapenem-resistant *Klebsiella*[a]	5.4 (1.7–17.1)	0.005	6.7 (2.4–18.8)	<0.001
Mechanical ventilation	4.9 (1.6–14.7)	0.005		NS[b]
Malignancy	3.9 (1.2–12.2)	0.02		NS

a After introduction of the McCabe score variable into the models, the isolation of CRKP remained an independent predictor of in-hospital mortality, albeit with a lower OR (for patients with CRKP versus those with CSKS, OR, 3.9; 95% CI, 1.1 to 13.6; *P* 0.03; for patients with CRKP versus controls, OR, 5.0; 95% CI, 1.7 to 14.8; *P* 0.004).
b NS, not significant.

Schwabe JJ ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2008, p. 1028–1033 Vol. 52, No. 3

Carbapenemase septicémie en hemato mortalité à 14j

Table 3. Multivariable analysis for 14 day mortality ($n=423$)[a]

Risk factor	Adjusted OR	95% CI	P
Propensity for carbapenem resistance	0.43	0.1–1.8	0.25
HSCT-CI			
low comorbidity	reference		1
intermediate comorbidity	1.03	0.48–2.21	0.94
high comorbidity	2.66	1.3–5.41	0.007
Last chemotherapy treatment			
autologous HSCT	0.37	0.11–1.21	0.1
salvage	1.98	0.91–4.31	0.09
other[b]	reference		1
Functional capacity at bacteraemia onset			
independent	reference		1
dependent	2.72	1.2–6.15	0.02
bedridden	5.94	2.78–12.71	<0.001
Septic shock	5.49	2.71–11.16	<0.001
Platelets[c]	0.94	0.87–1.01	0.09
Albumin[c]	0.52	0.28–0.95	0.03
Polymicrobial bacteraemia	2.35	1.15–4.81	0.02
CRGNB	5.14	2.32–11.38	<0.001

Andria N et al
Mortality burden related to infection with carbapenem-resistant Gram-negative bacteria among haematological cancer patients: a retrospective cohort study
J Antimicrob Chemother 2015; 70: 3146–3153

Carbapenemase septicémie en hemato mortalité à 1 an

Table 4. Cox regression analysis for 1 year mortality ($n=330$)[a]

Risk factor	HR	95% CI	P
Propensity for carbapenem resistance	1.01	0.45–2.27	0.97
Diabetes	1.81	1.25–2.63	0.002
Functional capacity prior to bacteraemia onset			
independent	reference		
dependent	1.74	1.18–2.57	0.006
bedridden	3.4	2.31–5	<0.001
Last chemotherapy treatment			
autologous HSCT	0.36	0.22–0.6	<0.001
salvage	1.63	1.12–2.38	0.01
other[b]	reference		
Admission-days before bacteraemia[c]	1.02	1.01–1.03	0.004
Mean arterial blood pressure[c]	0.87	0.78–0.96	0.006
Platelets[c]	0.95	0.92–0.98	<0.001
Albumin[c]	0.63	0.46–0.84	0.002
CRGNB	1.48	1–2.2	0.05

Andria N et al
Mortality burden related to infection with carbapenem-resistant Gram-negative bacteria among haematological cancer patients: a retrospective cohort study
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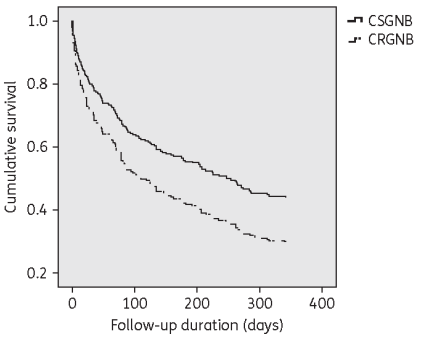


Figure 2. One year survival curves for patients with CRGNB and CSGNB. Cox adjusted $P=0.05$ (see Table 4 for variables included in the model).

Andria N et al
Mortality burden related to infection with carbapenem-resistant Gram-negative bacteria among haematological cancer patients: a retrospective cohort study
J Antimicrob Chemother 2015; 70: 3146–3153

Mortalité BLSE

	Death (n = 81)	Survival (n = 306)	p	RR (95 % CI)
Place of acquisition				
Community acquired	13 (16)	97 (31.7)	0.003	0.41 (0.22-0.78)
Health care associated	25 (30.9)	112 (36.6)	0.2	0.82 (0.53-1.24)
Nosocomial	43 (53.1)	97 (31.7)	<0.001	2 (1.36-2.93)
Origin of infection				
Urinary	38 (46.9)	177 (57.8)	0.05	0.71 (0.48-1.04)
Biliary	8 (9.9)	41 (13.4)	0.26	0.76 (0.39-1.47)
Unknown	9 (11.1)	28 (9.2)	0.36	1.18 (0.64-2.16)
Intra-abdominal	11 (13.6)	23 (7.5)	0.07	1.63 (0.96-2.77)
Pneumonia	8 (9.9)	20 (6.5)	0.21	1.41 (0.75-2.61)
Catheter	3 (3.7)	13 (4.2)	0.56	0.89 (0.32-2.52)

Peralta g et al
Impact of empirical treatment in extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp. bacteremia. A multicentric cohort study
BMC Infectious Diseases 2012, 12:245

Mortalité BLSE (2)

	Death (n = 81)	Survival (n = 306)	p	RR (95 % CI)
Comorbidity				
Diabetes	21 (25.9)	91 (29.7)	0.3	0.86 (0.55-1.34)
Ictus	15 (18.5)	55 (18)	0.51	1.03 (0.63-1.69)
Dementia	16 (19.8)	50 (16.3)	0.28	1.2 (0.74-1.93)
COPD	15 (18.5)	50 (16.3)	0.38	1.12 (0.69-1.84)
Chronic renal failure	20 (24.7)	48 (15.7)	0.05	1.54 (1-2.37)
Cardiac failure	15 (18.5)	41 (13.4)	0.16	1.34 (0.83-2.18)
Liver cirrhosis	16 (19.8)	28 (9.2)	0.009	1.92 (1.23-3)
Cancer	33 (40.7)	78 (25.5)	0.006	1.71 (1.17-2.51)
Metastatic tumor	13 (16)	20 (6.5)	0.009	2.05 (1.28-3.3)
Immunosuppression	16 (19.8)	49 (16)	0.25	1.22 (0.76-1.97)
Charlson ≥3	60 (74.1)	149 (48.7)	<0.001	2.43 (1.54-3.84)

Peralta g et al
Impact of empirical treatment in extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp. bacteremia. A multicentric cohort study
BMC Infectious Diseases 2012, 12:245

Mortalité BLSE (3)

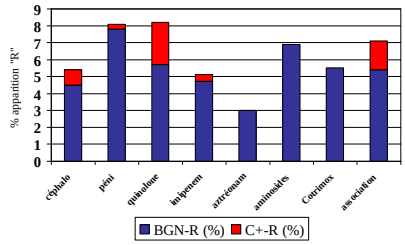
	Death (n = 81)	Survival (n = 306)	p	RR (95 % CI)
Microbiology				
E. coli	65 (80.2)	278 (90.8)	0.009	0.52 (0.33-0.82)
Multidrug resistant	45 (55.6)	132 (43.1)	0.03	1.48 (1-2.19)
Presentation				
Sepsis severe or shock	57 (70.4)	68 (22.5)	<0.001	4.9 (3.2-7.51)
Adequate empirical therapy	34 (42)	164 (53.6)	0.04	0.69 (0.47-1.02)
Adequate change for definitive therapy	29 (32.1)	109 (35.6)	0.33	0.88 (0.58-1.34)

Peralta g et al
Impact of empirical treatment in extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella spp. bacteremia. A multicentric cohort study
BMC Infectious Diseases 2012, 12:245

Apparition des résistances sous traitement

Tous les germes pathogènes étaient sensibles !!!!

Fish DN, Pharmacotherapy 1995;15(3):279-291) **14 000 patients !!!**



« Avant » les BLSE et meti-R et vanco…
« avant » les inhibiteurs de Base

Réponse bactériologique selon l 'apparition de résistance

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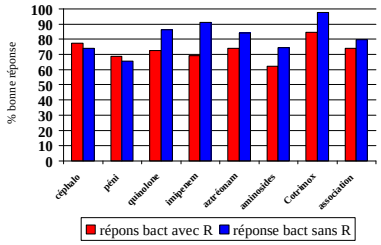
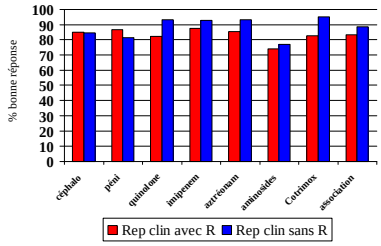


« Avant » les BLSE et meti-R et vanco…
« avant » les inhibiteurs de Base

Réponse clinique selon l 'apparition de résistance
Tous les germes pathogènes étaient sensibles !!!!

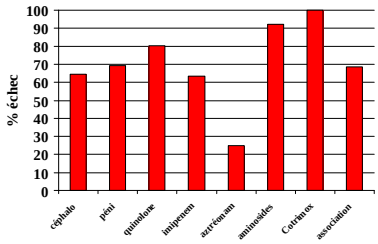
Fish DN, Pharmacotherapy 1995;15(3):279-291) **14 000 patients !!!**



« Avant » les BLSE et meti-R et vanco…
« avant » les inhibiteurs de Base

Echec d 'un 2eme traitement en présence d 'une résistance acquise (après un 1er TT)
Tous les germes pathogènes étaient sensibles !!!!

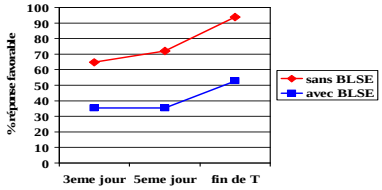
Fish DN, Pharmacotherapy 1995;15(3):279-291) **14 000 patients !!!**



« Avant » les BLSE et meti-R et vanco…
« avant » les inhibiteurs de Base

Mais quand c 'est « S » cela marche t il toujours

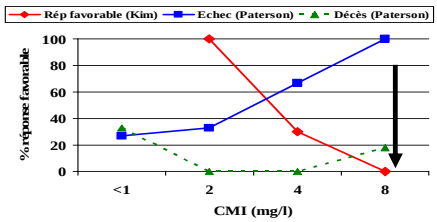
Septicémie BGN « sensible » in vitro
réponse « favorable » au traitement « que par C3G »



Kim YK, AAC 2002;46:1481-91

Mais quand c 'est « S » cela marche t il toujours

Septicémie BGN « sensible » in vitro
réponse « favorable » au traitement vs CMI



Kim YK, AAC 2002;46:1481-91
Paterson DL, JCM 2001;39:2206-12

Cephalo mono vs wild ou ebls – c'est la cmi qui compte

Andes et Craig 2005

Table 1. Clinical outcome in 42 patients with ESBL-producing *Klebsiella* spp. or *E. coli* bacteraemia and treated with cephalosporin monotherapy

Outcome	MIC ≤ 1 mg/L	MIC 2 mg/L	MIC 4 mg/L	MIC 8 mg/L
Success	81%	67%	27%	11%
Failure	19%	33%	73%	89%

Niveau de CMI piptaz vs E coli BLSE

Variable and group	All patients ($n = 39$)	Mortality in patients in each group[a]: 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	7/39 (17.9)	0/18 (0)[b]	3/10 (30)	4/7 (57.1)
Age				
≤65 years	4/20 (20)	0/9 (0)	1/5 (20)	3/6 (50)
>65 years	3/19 (15.8)	0/9 (0)	2/5 (40)	1/5 (20)
Onset				
Community	2/21 (9.5)	0/10 (0)	1/5 (20)	1/6 (16.7)
Nosocomial	5/18 (27.8)	0/8 (0)	2/5 (40)	3/5 (60)
Charlson index				
≤2	4/24 (16.7)	0/12 (0)	3/8 (37.5)	1/4 (25)
>2	3/15 (20)	0/6 (0)	0/2 (0)	3/7 (42.9)
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)		

Retamar P AAC 2013 57:3402

CMI 8 CEFEPIME

Table 2. Multivariate Logistic Regression Analysis of Associations Between Different Variables and 30-Day Mortality in the Definitive Therapy Cohort

Variable	Survivors (n = 141)	Nonsurvivors (n = 37)	Univariate Analysis OR (95% CI)	Univariate Analysis *P* Value	Multivariate Analysis OR (95% CI)	Multivariate Analysis *P* Value
Age, years (mean ± SD)	65.1 ± 17.1	69.7 ± 16.9	...	.15	...	...
Male	78 (55.1)	21 (56.8)	1.06 (.51–2.2)	1.0	...	...
Hospital-onset bacteremia	96 (68.1)	31 (83.8)	2.42 (.94–6.22)	.07	1.46 (.47–4.48)	.51
Urosepsis	38 (27.0)	1 (2.7)	0.08 (.01–.57)	.001	0.18 (.02–1.43)	.1
Pitt bacteremia score ≥4 points	85 (60.3)	34 (91.9)	7.47 (2.19–25.49)	<.001	5.36 (1.37–20.91)	.016
Rapidly fatal underlying disease	9 (6.4)	11 (29.7)	6.21 (2.34–16.47)	<.001	4.42 (1.54–12.64)	.006
Definitive therapy with cefepime	7 (5.0)	10 (27.0)	7.09 (2.48–20.27)	<.001	9.93 (2.77–31.91)	<.001

Data are given as number (percentage) unless otherwise specified. Ellipses indicate not available.

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation.

Lee NY et al
Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae: MIC Matters
Clinical Infectious Diseases 2013;56(4):488–95

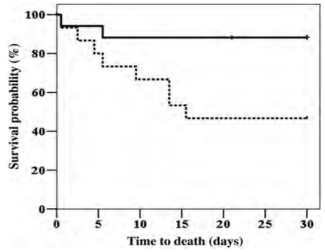


Figure 3. Kaplan-Meier survival analysis curves for patients with bacteremia caused by extended-spectrum ß-lactamase–producing organisms; bacteremia treated using a carbapenem (solid line) vs cefepime (broken line; log-rank test, $P = .016$).

Lee NY et al
Cefepime Therapy for Monomicrobial Bacteremia Caused by Cefepime-Susceptible Extended-Spectrum Beta-Lactamase–Producing Enterobacteriaceae: MIC Matters
Clinical Infectious Diseases 2013;56(4):488–95

E coli BLSE vs présentation (gravité) vs virulence

Table 3 Multivariate analysis of variables associated with 30-day mortality in patients with bacteraemia due to ESBL-producing *E. coli*.

Variable	OR (95% CI)	*p*
Charlson index	1.31 (1.10—1.53)	0.002
Source other than urinary tract	4.63 (2.01—10.61)	<0.001
Inappropriate empirical therapy	2.37 (1.06—5.31)	0.03
papGII	0.21 (0.04—0.97)	0.04
ibeA	3.54 (1.02—12.27)	0.04
Amoxicillin—clavulanate-resistant isolate	2.15 (0.98—4.71)	0.05

Mais l'impact du TT antibiotique disparait si la présentation est grave

Table 4 Multivariate analysis of variables associated with presentation with severe sepsis or septic shock in patients with bacteraemia due to ESBL-producing *E. coli*.

Variable	OR (95% CI)	*p*
Charlson index	1.42 (1.21—1.66)	<0.001
Neutropenia	3.73 (0.95—14.54)	0.05
High risk source (unknown, pneumonia)	2.13(1.04—4.37)	0.03
papGII	0.34 (0.10—1.14)	0.08

J. Rodri´guez-Ba–no et al Journal of Infection (2013) 67, 27e34

BLSE: E coli, Klebsielle et E cloacae

Variable	Mortality [no. of patients who died/total no. of patients (%)]	Unadjusted OR for mortality (95% CI) in univariable analysis	Adjusted OR for mortality[a] (95% CI) in multivariable analysis	
Appropriate therapy within <24 h				
Yes	16/85 (19)	1.12 (0.57–2.19)	1.53 (0.68–3.45)	antibio
No	30/146 (21)			
Charlson index				
<3	22/145 (15)	2.16 (1.13–4.16)*	2.80 (1.21–6.51)*	Co morbid
≥3	24/86 (28)			
Patient age (yr)				
<75	29/177 (16)	2.35 (1.17–4.72)*	3.81 (1.55–9.39)*	age
≥75	17/54 (31)			
LOS before onset (days)				
<21	33/169 (20)	1.09 (0.53–2.25)		
≥21	13/62 (21)			
Hospital ward at bacteremia onset				
Other	31/196 (19)	3.99 (1.85–8.64)*	2.88 (1.05–7.85)*	
ICU	15/35 (43)			
Bacteremia source				
UTI	8/96 (8)	4.31 (1.91–9.71)*	4.79 (1.74–13.16)*	site
Other	38/135 (28)			
Bacteremia origin				
CO	5/38 (13)	1.78 (0.65–4.85)		
HC	41/193 (21)			
Severe sepsis				
No	14/150 (9)	7.24 (3.53–14.71)*	5.24 (2.36–11.60)*	gravité
Yes	32/75 (43)			
Neutropenia				
No	40/206 (19)	1.31 (0.49–3.50)		
Yes	6/25 (24)			

Frakking F *AAC*. 2013, 57(7):3092

Impact d'un traitement antibiotique préalable (Johnson et al. 2011)

Table 4. Characteristics associated with specific Gram-negative species

	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	Antibiotic Reuse (n = 165)	Prior Antibiotics Without Reuse (n = 145)	Inappropriate Treatment (n = 235)	Appropriate Treatment (n = 519)	Hospital Mortality (n = 310)	Hospital Survival (n = 444)
Escherichia coli	42 (13.5)	190 (42.8)[a]	19 (11.5)	23 (15.9)	41 (17.4)	191 (36.8)[a]	74 (23.9)	158 (35.6)[a]
Klebsiella pneumoniae	73 (23.5)	102 (23.0)	35 (21.2)	38 (26.2)	42 (17.9)	133 (25.6)[a]	70 (22.6)	105 (23.6)
Pseudomonas aeruginosa	72 (23.2)	61 (13.7)[a]	38 (23.0)	34 (23.4)	42 (17.9)	91 (17.5)	71 (22.9)	62 (14.0)[a]
Acinetobacter species	41 (13.2)	22 (5.0)	24 (14.5)	17 (11.7)	44 (18.7)	19 (3.7)[a]	32 (10.3)	31 (7.0)
Polymicrobial bacteremia	20 (6.5)	36 (8.1)	7 (4.2)	13 (9.0)	11 (4.7)	45 (8.7)	16 (5.2)	40 (9.0)[a]

[a] $p < .05$. Values are expressed as number (%).

Table 5. Multivariate analysis of independent risk factors for hospital mortality[a]

Variable	Adjusted Odds Ratio	95% Confidence Interval	*p*
Prior antibiotic exposure	1.70	1.41–2.06	.005
Use of vasopressors	1.83	1.47–2.29	.006
Pseudomonas infection	1.75	1.39–2.21	.016
Inappropriate initial therapy	2.03	1.66–2.49	<.001
Acute Physiology and Chronic Health Evaluation II score (1-point increments)	1.13	1.11–1.15	<.001
Number of organ failures (one–organ increments)	1.93	1.73–2.14	<.001

"Other covariates not in the table had a p value >.05, including age, health care-associated hospital-onset infection, *Acinetobacter* infection, mechanical ventilation, in the intensive care unit when sepsis occurred, and the lungs as the source of infection (Hosmer-Lemeshow goodness-of-fit test, $p = .464$).

Impact of Inadequate Initial Antimicrobial Therapy on Mortality in Infections Due to Extended-Spectrum β-Lactamase–Producing EnterobacteriaceaeVariability by Site of Infection
Emily P. Hyle, BS; Adam D. Lipworth, BS; Theoklis E. Zaoutis, MD; Irving Nachamkin, DrPH, MPH; Warren B. Bilker, PhD; Ebbing Lautenbach, MD, MPH, MSCE
Arch Intern Med. 2005;165(12):1375-1380. doi:10.1001/archinte.165.12.1375

Table 2. Independent Risk Factors for Mortality (Multivariable Analysis)

Variable	Regression Coefficient (SE)	Adjusted OR (95% CI)	*P* Value
Inadequate antimicrobial therapy*	−0.36 (0.66)	0.69 (0.19-2.53)†	.58
APACHE II score	0.13 (0.04)	1.14 (1.05-1.24)‡	.002
Malignancy	1.60 (0.50)	4.96 (1.85-13.30)	<.001
Nonurinary infection	−1.30 (0.91)	0.27 (0.05-1.64)§	.16
Interaction between inadequate antimicrobial therapy and nonurinary infection	2.67 (1.08)		

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; OR, odds ratio.
*No treatment was given with an antibiotic to which the infecting organism was susceptible within 48 hours of the culture being sent.
†The OR is for subjects with urinary tract infections. The association between inadequate antimicrobial therapy and mortality for nonurinary infections was as follows: adjusted OR, 10.04; 95% CI, 1.90-52.96; $P = .007$.
‡The OR reflects the odds associated with each 1-point increase in APACHE II score.
§The OR is for subjects with adequate microbial therapy.

Mortalité des septicémies à Pyo à l'entrée à l'hopital

- Mortalité brute: 36%

Risk factors for in-hospital mortality — multivariable analysis[a]

Variable	OR (95% CI)	*P*
Severe sepsis or septic shock	21.9 (4.1–118.0)	<.001
High-risk source of bacteremia[b]	11.5 (2.3–57.4)	.003
Recent hospitalization (last 2 weeks)	6.2 (1.2–32.8)	.032
Poor functional status	5.8 (1.2–26.7)	.029

Inadequate empirical antimicrobial therapy	OR, 9.6	0.037
with severe sepsis	RR, 1.8	0.051
With septic shock	RR, 2.1	0.194

V. Schechner et al. / Diagnostic Microbiology and Infectious Disease 71 (2011) 38–45

Résistance ou non

La mortalité est guidée par

- Gravité de la présentation
- L'intensité des comorbidités
- Le site de l'infection
- L'adéquation: bactérie – antibactérien
  - Existence in vivo de la possibilité de l'effet antibactérien
    - Délai
    - adaptation
  - CMI vs concentration
    - Présomption de résistance
      - » Exposition préalable
      - » Prévalence connue

Résistance ou non: faire face

La mortalité est guidée par

- Gravité de la présentation → **Évaluation - réanimation**
- L'intensité des comorbidités → **Évaluation - compensation**
- Le site de l'infection → **Évaluation clinique – chirurgie ,,,**
- L'adéquation:
  - bactérie – antibactérien → **Évaluation clinique , interrogatoire**
    Organisation hospitalière
    - Existence in vivo de la possibilité de l'effet antibactérien
      - Délai
      - adaptation
    - CMI vs concentration
      - Présomption de résistance → **Évaluation clinique**
        Considération des données microbio, PK,,,
        - » Exposition préalable
        - » Prévalence connue

Regles

Table 1 Rules for initial antimicrobial treatment of infections in ICU to avoid antimicrobial resistance

Diagnostic	Perform immediate diagnostic test before starting new antimicrobials
Choosing antibiotics	Available guidelines
	Gram stain examination and molecular techniques may help with initial choice of molecules
	Previous knowledge about individual, unit, or hospital colonizing flora
	Combination therapy in Gram-negative infection may help to increase the spectrum (but is not recommended to decrease resistance)
	An antimicrobial stewardship team may help to define local procedures and provide individual advice
Conducting antimicrobial therapy	Use appropriate high initial antibiotic dosing
	Control the infection source (drainage, surgery) as quickly as possible
	In patients with documented infection de-escalate to the molecule with the narrowest spectrum and similar efficacy
Stopping rules	Discontinue antibiotics in patients with negative culture and no evidence of clinical infections
	Stop the antimicrobial therapy early in case of rapid improvement. A rapid decrease of the procalcitonin level may help

Timsit JF, Harbarth, Carlet
Intensive Care Med (2014) 40:1580
De-escalation as a potential way of reducing antibiotic use and antimicrobial resistance in ICU

Un diagnostic de sensibilité – résistance au plus tot

Diagnostic de sensibilité immédiat Fast (PCR)

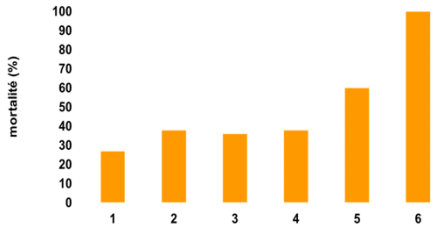
Table 2 Outcome parameters in the fast antibiotic susceptibility testing (FAST) versus standard of care (SOC) group among patients in which both identification (ID) and antibiotic susceptibility testing (AST) were performed

	FAST (n=114)	SOC (n=109)	p-Value
Mean time to Gram stain, in hours (SD)[a]	41.5 (21.0)	42.5 (20.3)	0.712
Mean time to results, in hours (SD)[a]	50.7 (21.0)	66.3 (20.1)	<0.001
Mean time to appropriate therapy, in hours (SD)[b]	28.2 (32.5)	26.9 (30.1)	0.962
Patients switched after FAST AST (n=12)	42.3 (13.3)		<0.001
Patients switched after SOC AST (n=34)		61.4 (14.7)	
Length of hospital stay, in days (range)	11 (0–75)	11 (1–133)	0.820
Patients switched after FAST AST (n=12)	13 (7–43)		0.486
Patients switched after SOC AST (n=34)		11 (1–133)	
Mortality (%)	12.3	7.3	0.216
Patients switched after FAST AST (n=12)	8.3		0.959
Patients switched after SOC AST (n=34)		8.8	

Beuving J et al
Impact of same-day antibiotic susceptibility testing on time to appropriate antibiotic treatment of patients with bacteraemia: a randomised controlled trial
Eur J Clin Microbiol Infect Dis (2015) 34:831

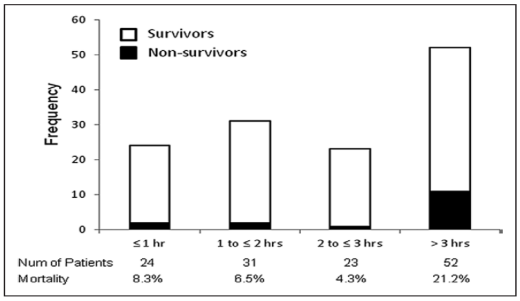
Un délai d'instauration d'un traitement
court mais précipitation

Délai de l'antibiothérapie



David F. Gaieski et al
Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal directed therapy was initiated in the emergency department
Crit Care Med 2010; 38:1045–1053

Délai antibio enfants



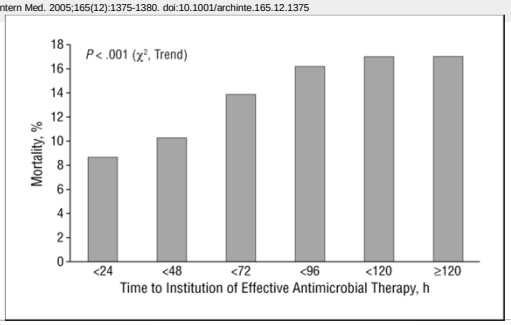
Time from sepsis recognition to initial antimicrobial administration with survival fraction. Total number of patients at hourly intervals from sepsis recognition to administration of initial antimicrobial therapy. The shaded portion of each bar indicates the number of nonsurvivors in each time interval

Weiss SL et al
Delayed Antimicrobial Therapy Increases Mortality and Organ Dysfunction Duration in Pediatric Sepsis
Crit Care Med 2014; 42:2409–2417

The JAMA Network

From: **Impact of Inadequate Initial Antimicrobial Therapy on Mortality in Infections Due to Extended-Spectrum β-Lactamase–Producing Enterobacteriaceae: Variability by Site of Infection**

Arch Intern Med. 2005;165(12):1375-1380. doi:10.1001/archinte.165.12.1375



Delay in initial antimicrobial therapy and mortality.

Délai: ordre de grandeur

Hazard ratios for in-hospital mortality according to age, sex and times from triage to antibiotic administration – uncomplicated sepsis (n = 102)

	Hazard ratio for mortality	95% confidence interval	*P* value
Age (years)	1.09	1.03–1.15	0.002
Sex (male)	0.54	0.18–1.67	0.29
Time from triage to antibiotics			
≤1 h (*n* = 6)	1		
1–3 h (*n* = 31)	1.65	0.19–14.10	0.65
3–6 h (*n* = 35)	0.67	0.07–6.19	0.72
>6 h (*n* = 30)	0.57	0.06–5.70	0.63

Hazard ratios for in-hospital mortality according to age, sex and times from triage to antibiotic administration – severe sepsis (n = 118)

	Hazard ratio for mortality	95% confidence interval	*P* value
Age (years)	1.02	11.00–1.05	0.04
Sex (male)	2.23	1.16–4.28	0.02
Time from triage to antibiotics			
≤1 h (*n* = 21)	1		
1–3 h (*n* = 41)	1.49	0.58–3.86	0.41
3–6 h (*n* = 26)	1.50	0.53–4.25	0.44
>6 h (*n* = 30)	2.25	0.91–5.59	0.08

WISDOM A et al
INITIAT-E D.: Impact of timing of INITiation of Antibiotic Therapy on mortality of patients presenting to an Emergency Department with sepsis
Emergency Medicine Australasia (2015) **27**, 198–201

Les patients infectés hospitalisés ou en institution reçoivent un traitement adapté plus tard que les patients atteints d'infection communautaire

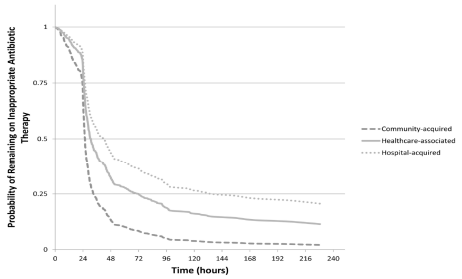


Figure 2. Probability of remaining on inappropriate antibiotic therapy based on Cox proportional hazards model. Healthcare exposure categories include community-acquired (dashed dark-gray line), healthcare-associated (solid light-gray line), and hospital-acquired (dotted light-gray line). Model inputs to produce these curves were the following: Charlson index of 0, malignancy=none, age >65, Medicare/Medicaid=yes, dependent in >3 activities of daily living=yes.

doi: 10.1371/journal.pone.0076225.g002

Moehring RW, Sloane R, Chen LF, Smathers EC, Schmader KE, et al. (2013) Delays in Appropriate Antibiotic Therapy for Gram-Negative Bloodstream Infections: A Multicenter, Community Hospital Study. PLoS ONE 8(10): e76225. doi:10.1371/journal.pone.0076225

Arch Intern Med. 2005;165(12):1375-1380. doi:10.1001/archinte.165.12.1375

Table 1. Risk Factors for Mortality (Bivariable Analysis)

Variable	Mortality, No./Total No. (%)	OR (95%CI)	*P* Value*
Inadequate antimicrobial therapy†			
Yes	24/112 (21.4)	2.28 (0.92-6.24)	.06
No	9/75 (10.7)		
Race (African American)			
Yes	9/85 (10.6)	0.44 (0.15-1.21)	.07
No	13/61 (21.3)		
Nursing home residence			
Yes	5/50 (10.0)	0.45 (0.13-1.30)	.12
No	27/137 (19.7)		
Health care acquisition of infection			
Yes	32/166 (19.3)	. . .	.03
No	0/21		
APACHE II score, median (range)†			
Among deceased	13 (6-29)		<.001
Among survivors	10 (0-26)		
ICU location at time of infection			
Yes	24/68 (35.3)	7.36 (2.89-20.23)	<.001
No	8/116 (6.9)		
Duration of hospitalization, median (range)‡			
Among deceased	12 (0-239)		.009
Among survivors	3.5 (0-150)		
Site of infection			
Nonurinary	20/88 (22.7)	2.13 (0.91-5.12)	.05
Urinary tract	12/99 (12.1)		
Malignancy			
Yes	12/31 (38.7)	4.26 (1.61-10.87)	.001
No	20/155 (12.9)		
Central venous catheter			
Yes	23/91 (25.3)	3.51 (1.40-9.61)	.003
No	9/91 (8.8)		
Urinary catheter			
Yes	26/136 (19.1)	2.08 (0.72-7.36)	.15
No	5/49 (10.2)		
Mechanical ventilation			
Yes	22/47 (46.8)	11.35 (4.45-29.86)	<.001
No	10/139 (7.2)		

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; ellipses, not calculable.
*Fisher exact test (categorical variables); Wilcoxon rank sum test (continuous variables). Only variables for which bivariable *P*<.20 are shown.
†No treatment was given with an antibiotic to which the infecting organism was susceptible within 48 hours of the culture being sent.
‡Days from hospital admission until infection with extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella* species.

Adequation ab et deces dans la vraie vie

Sepsis severe et choc septique

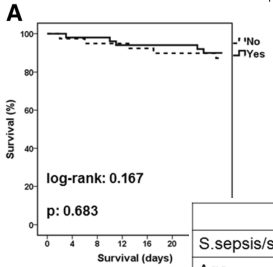
Variables	Survival (N = 908)	Death (N = 371)	Univariate analysis				Multivariate analysis			
			OR	CI 95%		P	OR	CI 95%		p
	N (%)	N (%)		Min	Max			Min	Max	
Age (years), mean ± SD	65.9±16	69.2±18	1.010	1.003	1.017	**0.004**	1.004	0.997	1.012	0.263
APACHE II, mean ± SD	16.2±9	21.8±10	1.060	1.046	1.074	**<0.001**	1.052	1.037	1.067	**<0.001**
Liver dysfunction	48 (5.2)	20 (5.3)	1.021	0.597	1.745	0.940				
Cardiac dysfunction	595 (97.8)	267 (77.3)	1.797	1.360	2.376	**<0.001**	1.439	1.048	1.976	**0.025**
Renal dysfunction	307 (33.8)	204 (54.9)	2.391	1.869	3.060	**<0.001**	1.792	1.371	2.341	**<0.001**
Hematologic dysfunction	307 (33.8)	155 (41.7)	1.405	1.096	1.800	**0.007**	1.684	1.270	2.234	**<0.001**
Respiratory dysfunction	576 (63.4)	255 (68.7)	1.267	0.979	1.640	**0.072**	1.693	1.265	2.266	**<0.001**
Neurologic dysfunction	283 (31.2)	142 (38.2)	1.369	1.064	1.762	**0.015**	1.286	0.976	1.694	0.073
Blood cultures prior to antibiotic administration	830 (91.4)	286 (77.0)	0.316	0.226	0.442	**<0.001**	0.380	0.264	0.546	**<0.001**
Broad-spectrum antibiotic within 1 hour	585 (64.4)	206 (55.5)	0.689	0.539	0.881	**0.003**	0.771	0.599	1.010	0.060
Serum arterial lactate	884 (97.4)	350 (94.3)	0.452	0.249	0.823	**0.009**	1.383	1.037	1.845	**0.027**
Central venous oxygen saturation	493 (54.3)	255 (68.7)	1.850	1.433	2.389	**<0.001**	0.392	0.203	0.757	**0.005**

Yokota PKO, Marra AR, Martino MDV, Victor ES, Dura˜o MS, et al. (2014) Impact of Appropriate Antimicrobial Therapy for Patients with Severe Sepsis and Septic Shock – A Quality Improvement Study. PLoS ONE 9(11): e104475.

La descalade ne pénalise pas le patient !

Desecalade: pas de pénalité pour les patients

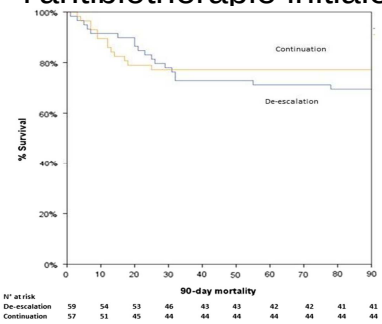
A



	HR	95%CI	p
S.sepsis/shock	29.03	3.69-228.62	0.001
Age	1.00	0.96-1.05	0.867
Gender	0.58	0.19-1.84	0.357
≥1 disease	2.60	0.71-9.57	0.151
De-escalation	2.48	0.75-8.12	0.134

Koupetori et al. BMC Infectious Diseases 2014, 14:272
Bloodstream infections and sepsis in Greece: over-time change of epidemiology and impact of de-escalation on final outcome

Descalade ou maintien de l'antibiothérapie initiale



Leone M et al papazian
De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial
Intensive Care Med (2014) 40:1399–1408

Descalade ou maintien (2)

Duration	De-escalation group ($n = 59$)	Continuation group ($n = 57$)	P
Duration of ICU stay (days)			
From inclusion to discharge	15.2 ± 15.0 9 [1–79]	11.8 ± 12.6 8 [1–60]	0.71
From admission to discharge	29.1 ± 50.0 13 [1–375]	18.1 ± 15.7 12 [3–67]	0.11
Number of ICU-free days[a]	13.2 ± 10.6 18 [0–23]	15.0 ± 11.3 21 [0–25]	0.21
Ventilator-free days[a]	18.9 ± 11.6 23 [6–29]	19.3 ± 11.8 26 [6–29]	0.55
Catecholamine free days[a]	22.3 ± 10.3 28 [21–29]	21.6 ± 11.2 28 [16–29]	0.93
Number of antibiotic days	14.1 ± 13.4 9 [7–15]	9.9 ± 6.6 7.5 [6–13]	0.04
Number of companion antibiotic days	2.3 ± 0.8 2.0 [2.0–3.0]	3.2 ± 1.7 3.0 [2.8–3.0]	<0.00
Number of antibiotic days for the initial episode	7.9 ± 5.2	8.0 ± 4.3	0.94
Number of antipseudomonal agent-free days[a]	23.6 ± 9.2 29 [24–29]	20.1 ± 9.6 24 [15–28]	<0.001
Number of carbapenem-free days[a]	25.6 ± 7.3 29 [26–29]	23.5 ± 8.4 29 [19–29]	0.17
Number of anti-MRSA drug-free days[a]	25.8 ± 7.1 29 [27–29]	24.1 ± 8.4 29 [21–29]	0.30

Leone M et al papazian
De-escalation versus continuation of empirical antimicrobial treatment in severe sepsis: a multicenter non-blinded randomized noninferiority trial
Intensive Care Med (2014) 40:1399–1408

Desecalade antibiotique vs neutropenie fébrile

Desescalade	HR décès
à M1	0,51 [0.20–1.33]
à 1 an	1,06 [0.54–2.08]

Mokart D et al
De-escalation of antimicrobial treatment in neutropenic patients with severe sepsis: results from an observational study
Intensive Care Med (2014) 40:41–49

Un traitement efficace

- La surenchère ne profite à personne
- ⇔ l'angoisse des docteurs ne se soigne pas par l'antibiothérapie des patients !

Pneumonies communautaires admises en réanimation
1 ou 2 pour commencer
a+b ?= a ou b ? Si a ou b efficace

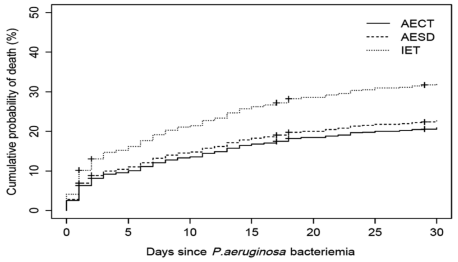
Table 4 Factors associated with 60-day mortality in the groups given monotherapy or dual therapy

Multivariate analysis	sHR	95% CI	*P*-value
Dual therapy versus monotherapy	1.14	0.86 to 1.50	0.37
SAPSII (per 10 points)	1.66	1.54 to 1.79	<.0001
Female gender	0.72	0.53 to 0.96	0.03
≥One co-morbidity	1.43	1.07 to 1.91	0.01
Antibiotic therapy on Day 2 versus Day 1	1.38	0.98 to 1.93	0.07
Antibiotic therapy on Day 3 versus Day 1	1.28	0.75 to 2.19	0.36
Steroids	0.97	0.71 to 1.32	0.83
Multivariate sensitivity analysis*	**sHR**	**(95% CI)**	***P*-value**
Restricted to *Streptococcus pneumoniae* infection	1.42	0.73 to 2.77	0.31
Restricted to documented infection	1.29	0.89 to 1.89	0.18
Restricted to patients with septic shock	1.11	0.75 to 1.64	0.59

*Adjusted on SAPSII, female gender, at least one co-morbidity, day of antibiotic therapy initiation and use of steroids.

Adrie et al. Critical Care 2013, 17:R265
Initial use of one or two antibiotics for critically ill patients with community-acquired pneumonia: impact on survival and bacterial resistance

Meme pour le pyo:
au moins 1 et 1 suffit



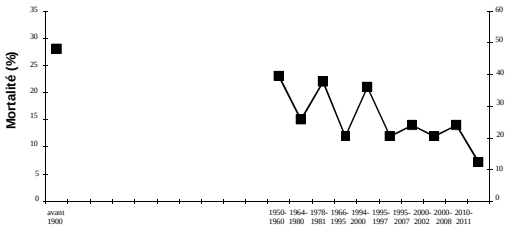
Cumulative risk of death for patients receiving adequate empirical antimicrobial therapy adjusted by Pitt score. Abbreviations: AECT, adequate empirical combination therapy; AESD, adequate empirical single-drug therapy; IET, inadequate empirical therapy.

Peña C et al
Effect of Adequate Single-Drug vs Combination Antimicrobial Therapy on Mortality in Pseudomonas aeruginosa Bloodstream Infections: A Post Hoc Analysis of a Prospective Cohort
Clinical Infectious Diseases 2013;57(2):208–16

Quand un traitement existe, la résistance n'est pas forcément péjorative

- Exemples
  - pneumonies à pneumocoque
  - Méningites à pneumocoque
  - BLSE

Pneumonie : mortalité « fin XIX-XXI »



Rueda AM et al. Medicine 2010;89:331.
Austrian R et al. Ann Intern Med. 1964;60:759.
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Redelings MD et al. Public Health Reports / March–April 2005 / Volume 120
Osler W. Practice of Medicine In Appleton and Co. 1892.
Osler W. Am J Med Sci 1897.

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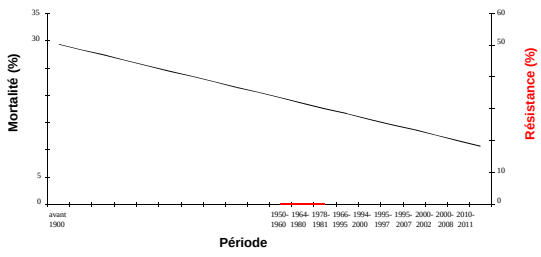
Pneumonie : mortalité résistance



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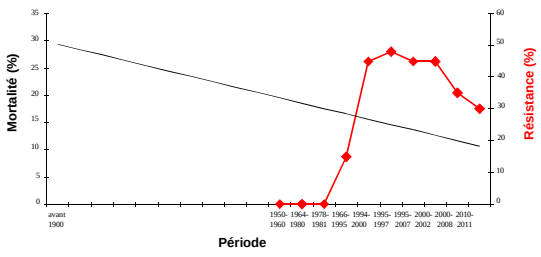
Pneumonie : mortalité résistance



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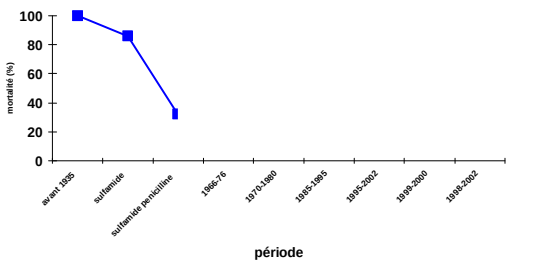
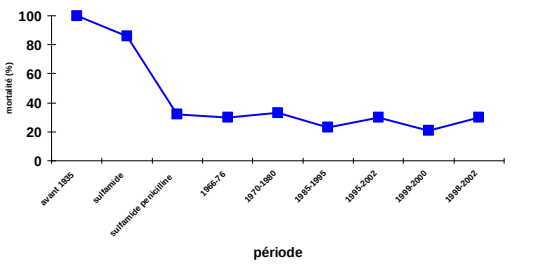
Méningite à pneumocoque adulte « pays riches » : mortalité



Jackson WPU et al. Arch Dis Child. 1949:22. • Bohr V et al. J Infect. 1985;10:143-57. • Bruyn GA et al. Eur J Clin Microbiol Infect Dis. 1989;8:695-700. • Almirante B et al. Med Clin (Barc). 1995;105:681-6. • Weisfelt M et al. Lancet Neurol. 2006;5:123-9. • Østergaard C et al. BMC Infectious Diseases 2005;5:93. • van de Beek D et al. N Engl J Med 2004;351:1849-59.

Méningite à pneumocoque adulte « pays riches » : mortalité



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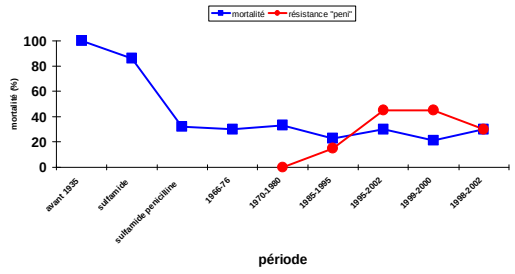

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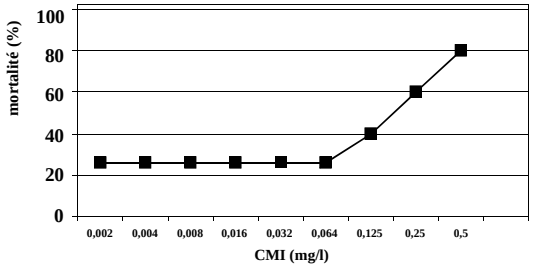
Mortalité vs CMI pneumocoque



Gouveia EL et al. Clinical outcome of pneumococcal meningitis during the emergence of penicillin-resistant Streptococcus pneumoniae: an observational study. BMC Infectious Diseases 2011;11:323.

BMR : quand le TT existe

Clinical Outcomes According to Sepsis Severity and Survival Status

Outcome	Sepsis	Severe Sepsis	Septic Shock	Survivors	Nonsurvivors
30-d mortality, % (*n*)	3.5 (6)	9.9 (19)[a]	28.6 (42)[ab]		
Length of stay, d	9.2 ± 9.4	15.3 ± 14.7[a]	20.8 ± 22.6[ab]	15.1 ± 17.2	13.1 ± 12.5
Length of ICU stay, d	2.5 ± 7.6	4.8 ± 10.9[a]	9.8 ± 13.2[ab]	5.4 ± 11.4	6.1 ± 8.5[c]
Number of procedures	2.2 ± 2.1	3.2 ± 3.3[a]	5.5 ± 3.9[ab]	3.4 ± 3.5	3.9 ± 3.3
Multidrug resistance, % (*n*)	18.0 (31)	17.8 (34)	23.1 (34)	19.2 (85)	20.9 (14)

Jason P. Burnham, Michael A. Lane, Marin H. Kollef
Impact of Sepsis Classification and Multidrug-Resistance Status on Outcome Among Patients Treated With Appropriate Therapy
Crit Care Med 2015; 43:1580–1586

Si la prévalence de la résistance est forte, le choix se porte sur un spectre large

- Exemple des infections urinaires fébriles

Empirical therapies among adults hospitalized for community-acquired upper urinary tract infections: A decision-tree analysis of mortality, costs, and resistance

J.J. Parienti JJ et al
Empirical therapies among adults hospitalized for community-acquired upper urinary tract infections, A decision-tree analysis of mortality, costs, and resistanceAmerican Journal of Infection Control xxx (2015) e53-e59

to evaluate the effectiveness, ecologic impact, and cost-effectiveness of different empirical antibiotic therapies administered to patients hospitalized for UTIs.

- (1) ceftriaxone (CRO) plus a single dose of gentamicin in the ICU;
- (2) imipenem (IMP) (avec desescalade si possible); and
- (3) an individualized empirical strategy based on a patient's clinical risk factors, restricting IMP use to patients at risk for harboring ESBL-producing Escherichia coli
  - Tumbarello
  - 2 major risk factors (3 points),
    - prior hospitalization <12 months
    - admission from another health care facility)
  - 4 minor risk factors (2 points)
    - a Charlson comorbidity score 4,
    - b-lactam or quinolone use <3 months,
    - Urinary catheter <30 days,
    - age 70 years).
  - Risque en ICU si score > 3 et en médecine > 6

- J.J. Parienti JJ et al
- Empirical therapies among adults hospitalized for community-acquired upper urinary tract infections, A decision-tree analysis of mortality, costs, and resistanceAmerican Journal of Infection Control xxx (2015) e53-e59

Cout – efficacité vs E coli

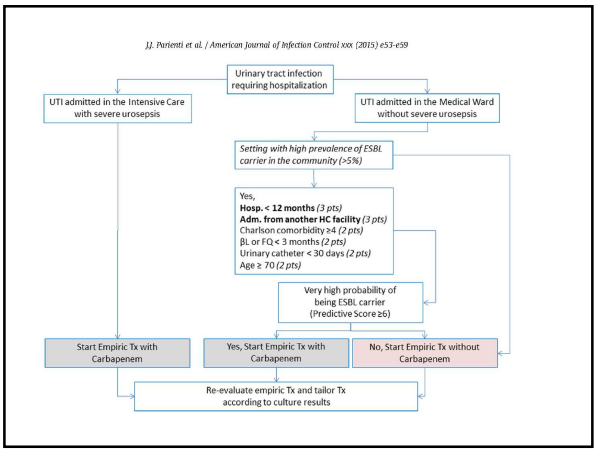
- Pour les patients en SI ou réa
  - La stratégie « ceftriaxone » est plus couteuse que la stratégie « imipenem » en raison de l'allongement de la durée d'hospitalisation secondaire à l'inadéquation thérapeutique en cas de BLSE
  - La stratégie Imipenem est légèrement plus efficace
    - Une vie gagnée pour 556 patients traités
- Pour les patients en médecine
  - L'efficacité Ceftriaxone et imipenem sont identiques
  - La stratégie imipenem est moins couteuse que ceftriaxone genta

Risque de résistance aux penem vs E coli

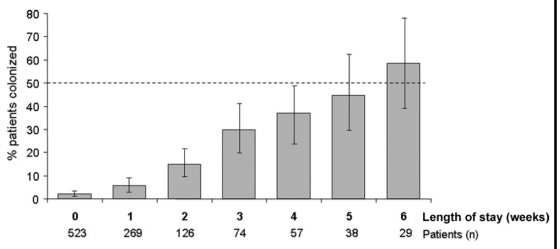
- Si imipenem à tout le monde
  - OR + 4,9 par rapport à la stratégie ceftriaxone
  - OR + 1,9 si considération du score de risque

Effect of empirical anti-*Escherichia coli* therapies on carbapenem resistance

Patients in the MW		Patients in the ICU		Absolute odds ratio	Relative odds ratio
Empirical CRO	-- et --	Empirical CRO	→	1.35	1.00 (Ref.)
Empirical CRO	-- et --	Empirical CRO or IMP†	→	1.40	1.04
Empirical CRO	-- et --	Empirical IMP	→	1.49	1.11
Risk factor–based CRO or IMP*	-- et --	Risk factor–based CRO or IMP†	→	1.63	1.21
Risk factor–based CRO or IMP*	-- et --	Empirical IMP	→	1.72	1.28
Empirical IMP	-- et --	Empirical IMP	→	6.10	4.52



Selection en réa par l'imipenem



Laurence Armand-Lefèvre AAC 2013 57:1488

Selection en réa par l'imipenem

TABLE 1 Mechanisms of resistance and MICs for imipenem and ertapenem of 56 isolated imipenem-resistant Gram-negative bacilli

Species	No. of strains	Resistance mechanisms[a]		MIC (mg/liter)[b]	
		Enzymes	Other	Imipenem	Ertapenem
P. aeruginosa	19		OprD−	6–>32	ND
	6	AmpC++	OprD−	16–>32	ND
	4		OprD− MexAB efflux++	24–>32	ND
	2	AmpC++	OprD− MexAB efflux++	24–32	ND
	1	GES-9	OprD−	>32	ND
	4	VIM-2		>32	ND
Enterobacteriaceae					
K. pneumoniae	2	DHA-1	OMP−	24–32	>32
	1	TEM-1 CTX-M15	NP	3	>32
E. aerogenes	1	TEM-24 AmpC++	OMP−	16	>32
E. cloacae	1	SHV-12 AmpC++	OMP−	32	>32
H. alvei	1	AmpC++	NP	4	32
A. baumannii	2			6–12	ND
S. maltophilia	12	Wild type		ND	ND

[a] OprD−, loss of OprD porin; AmpC++, hyperexpression of AmpC chromosomal cephalosporinase; MexAB efflux++, hyperexpression of MexAB-OprM system efflux; OMP−, loss or reduced expression of outer membrane protein; NP, OMP analysis not performed.
[b] ND, not determined.

Laurence Armand-Lefèvre AAC 2013 57:1488

Selection en réa par l'imipenem

TABLE 2 Univariate and multivariate analysis of risk factors associated with intestinal colonization of imipenem-resistant Gram-negative bacilli[a]

Characteristic or outcome	No. of individuals or parameter value (%, unless range is specified)				
	Carrier patients (n = 36)	Controls (n = 36)	Univariate OR[b]	Univariate P[c]	Multivariate OR[d]
Antibiotic treatments					
Exposure time to antibiotics, days [median (range)]	11.5 (0–51)	9.0 (0–37)		0.84	
Penicillin exposure	8 (22.2)	16 (44.4)	0.4 (0.1–1.1)	0.08	0.3 (0.1–0.8)
Penicillin and β-lactamase inhibitor exposure	17 (47.2)	20 (55.6)	0.7 (0.3–2.0)	0.64	
Cephalosporin exposure	20 (55.6)	17 (47.2)	1.4 (0.5–3.9)	0.64	
Imipenem exposure	28 (77.8)	14 (38.9)	5.4 (1.8–17.8)	<0.01	
Days of imipenem exposure				<0.01	
0	8 (22.2)	22 (61.1)	1.0		1.0
1 to 3	10 (27.8)	6 (16.7)	4.4 (1.1–20.5)		5.9 (1.5–25.7)
4 to 21	18 (50.0)	8 (22.2)	6.0 (1.7–23.3)		7.8 (2.4–29.8)
Fluoroquinolone exposure	9 (25.0)	8 (22.2)	1.2 (0.3–4.0)	1.00	
Aminoglycoside exposure	25 (69.4)	21 (58.3)	1.6 (0.6–4.8)	0.46	
Glycopeptide exposure	20 (55.6)	11 (30.6)	2.8 (1.0–8.4)	0.06	
Metronidazole exposure	5 (13.9)	6 (16.7)	0.8 (0.2–3.6)	1.00	
Macrolide exposure	5 (13.9)	3 (8.3)	1.8 (0.3–12.3)	0.71	
Colistin exposure	5 (13.9)	2 (5.6)	2.7 (0.4–30.4)	0.43	

Laurence Armand-Lefèvre AAC 2013 57:1488

En guise de:

La concomittance des résistances et de l'absence de nouveautés thérapeutiques impose « de revisser les boulons »

Dans « un » hopital de France 2014 (1)

- 100 septicémies
- Adéquation antibiothérapie probabiliste: 65%
- Délai d'efficacité antibiotique: 15h
  - 60% 1h
- Adéquation antibiothérapie infection documentée: 79%
- Desescalade « oubliée »: 30%
- Implication d'un infectiologue: 30%

100 septicémies dans « un » hopital de France 2014 (2): **Devenir**

- **20% de décès au CH**
  - 11% à J10
  - 16% à J28
- **Caractéristiques**
  - Moyenne d'âge de 75 ans
  - Comorbidités (néoplasie évolutive, démence avancée…)
  - Présentation
    - 50% en sepsis grave, 20% en choc septique, et 30% en sepsis non grave
  - 33% de BMR (versus 15% chez les patients vivants)
  - 50% d'ABT probabiliste inadaptée (versus 26%)

Dans « un » hôpital de France