

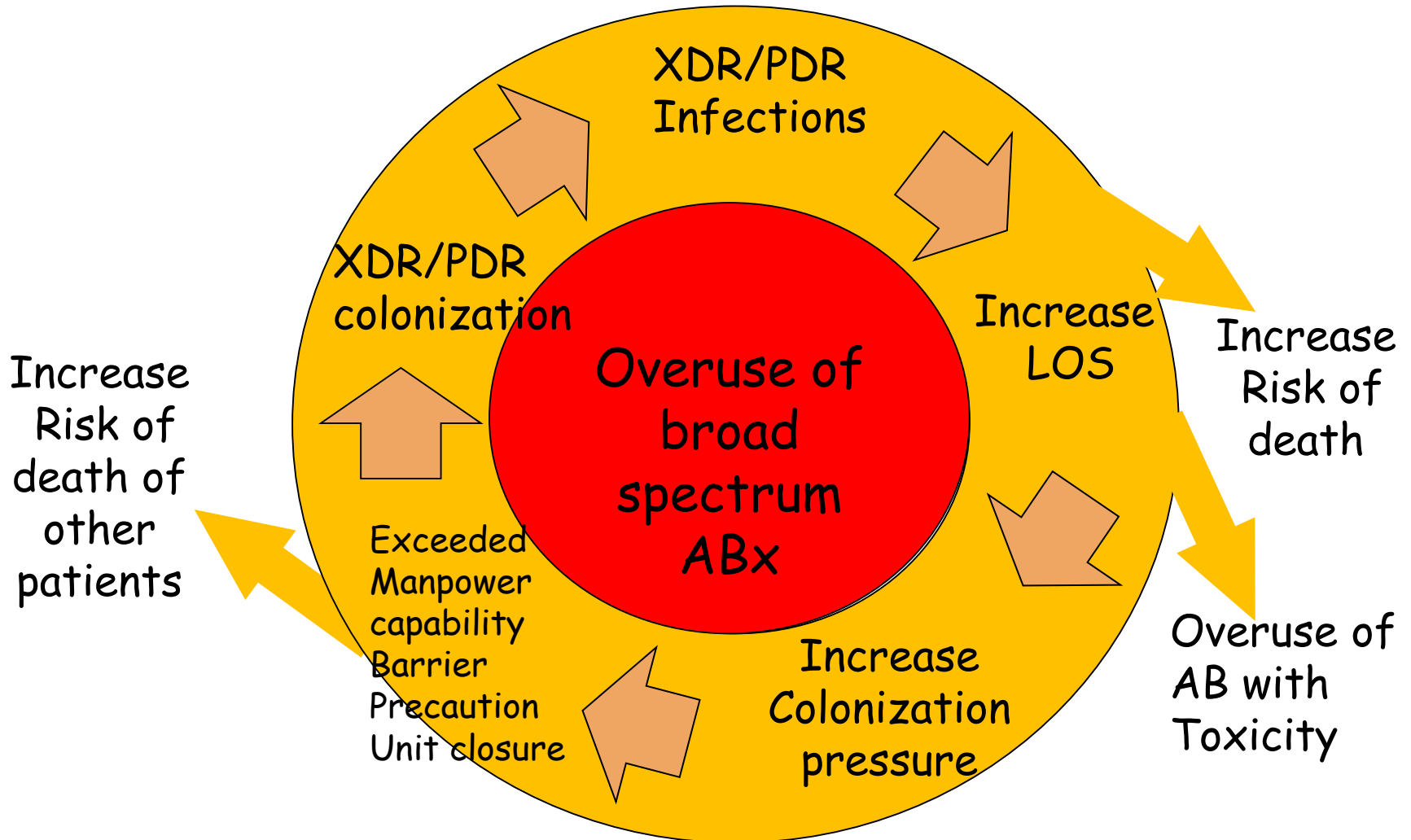


Coût (morbidité mortalité) de la résistance bactérienne aux antibiotiques

Jean-François Timsit MD PhD
Réanimation médicale et infectieuses
APHP-Hôpital Bichat
Inserm UMR 1137 IAME
Université Paris-Diderot



The vicious circle



Potential impact of bacterial resistance

Friedman et al - CMI 2016

The effect	Examples
Morbidity and mortality	All-cause Attributable to infection Increased length of hospital stay Increased length of mechanical ventilation Increased need for intensive care and invasive devices Excess surgery Functional decline and need for post-acute care Need for contact isolation Loss of work
Increased resource utilization and cost	Hospital, intensive-care unit and post-acute care beds Additional nursing care, support services, diagnostic tests and imaging Additional use of isolation rooms and consumables (gloves, gowns) Cost of targeted infection control programmes including screening and isolation
Guideline alterations	Loss of narrow-spectrum antibiotic classes Altered empiric therapy regimens Use of agents with reduced efficacy Use of agents with increased toxicity
Reduced hospital activity	Unit closures Cancellation of surgery

Common pitfalls

- Severity
- Previous medical history
- Previous antimicrobials
- Procedure use
- Duration of hospital stay prior to NI
- Competing risks: discharge is an informative censor

an individual discharged from hospital at time t could not be considered as exposed to the same risk of acquisition of NI and death at $t+1$ as other patient still in the hospital... .

Klebsiella pneumoniae BSIs

Ben-David CMI 2012

Variable		SKP (n = 85)	ESBLKP (n = 65)	CRKP (n = 42)	p
Demographic characteristics and co-morbidities	Male (%)	48 (57)	35 (54)	28 (67)	0.4
	Age, years, median (IQR)	71 (28)	73 (22)	73 (27)	0.97
	Previous hospitalizations during prior 12 months (%)	40 (47)	39 (60)	23 (55)	0.28
	Charlson score, median (IQR)	3 (4)	3 (4)	3 (3)	0.47
	Co-morbidities (%)				
	Myocardial infarction	13 (17)	6 (11)	8 (19)	0.45
	Chronic heart failure	18 (23)	4 (7)	11 (26)	0.02
	Stroke	16 (20)	19 (33)	7 (17)	0.11
	Dementia	7 (9)	7 (12)	5 (12)	0.79
	Chronic lung disease	7 (9)	11 (19)	6 (14)	0.23
	→ Peptic ulcer	1 (1)	5 (9)	11 (26)	0.001
	Diabetes mellitus	27 (34)	19 (33)	15 (36)	0.95
	Chronic renal failure	16 (21)	13 (23)	16 (39)	0.07
	Malignancy	35 (42)	21 (33)	8 (19)	0.04
Hospital events prior to onset of infection	LOS before BSI, median days (IQR)	8 (16)	16 (22)	12 (26)	0.019
	Nosocomial acquisition (%)	67 (79)	62 (95)	42 (100)	0.001
	→ ICU stay (%)	18 (21)	21 (32)	24 (57)	<0.001
	→ Urinary catheter (%)	34 (40)	41 (63)	31 (74)	<0.001
	→ Central venous catheter (%)	22 (26)	19 (29)	21 (50)	0.019
	Surgical procedure (%)	24 (28)	24 (37)	17 (41)	0.32
	→ Dialysis (%)	2 (2)	5 (8)	7 (17)	0.014
	Other patients with CRKP on the ward (%)	37 (44)	23 (35)	31 (74)	<0.001
	→ Nosocomial pneumonia (%)	11 (13)	18 (28)	16 (38)	0.004
	Surgical site infection (%)	2(2)	5 (8)	5 (12)	0.09
	Prior antimicrobial treatment (%)	27 (32)	45 (70)	38 (91)	<0.001
	→ Fluoroquinolones	6 (7)	21 (32)	19 (45)	<0.001
	→ Carbapenem	5 (6)	12 (18)	11 (26)	0.006
	→ Cephalosporin	8 (9)	13 (20)	21 (50)	<0.001
→ Pipril tazobactam	27 (32)	45 (70)	38 (91)	<0.001	
Events on the onset of BSI	Pitt bacteraemia score, median (IQR)	2 (4)	3 (5)	4 (5)	0.002
	→ Appropriate antibiotic empirical therapy (%)	67 (79)	25 (39)	5 (12)	<0.001

Klebsiella pneumoniae BSIs

Ben-David CMI 2012

TABLE 2. Outcome of patients with *K. pneumoniae* bloodstream infections

Variable	S-KP (n = 85)	ESBL-KP (n = 65)	CRKP (n = 42)	p
In-hospital mortality (%)	20 (24)	25 (39)	29 (69)	<0.001
Infection-related mortality (%)	14 (17)	14 (22)	20 (48)	0.001
LOS after infection, median days (IQR)	9 (16)	16 (34)	18 (22)	0.003
Total LOS, median days (IQR)	21 (36)	36 (70)	37 (31)	0.001

CRKP, carbapenem-resistant *K. pneumoniae*; ESBLKP, extended-spectrum beta lactamase-producing *K. pneumoniae*; IQR, interquartile range; LOS, length of stay; SKP, susceptible *K. pneumoniae*.

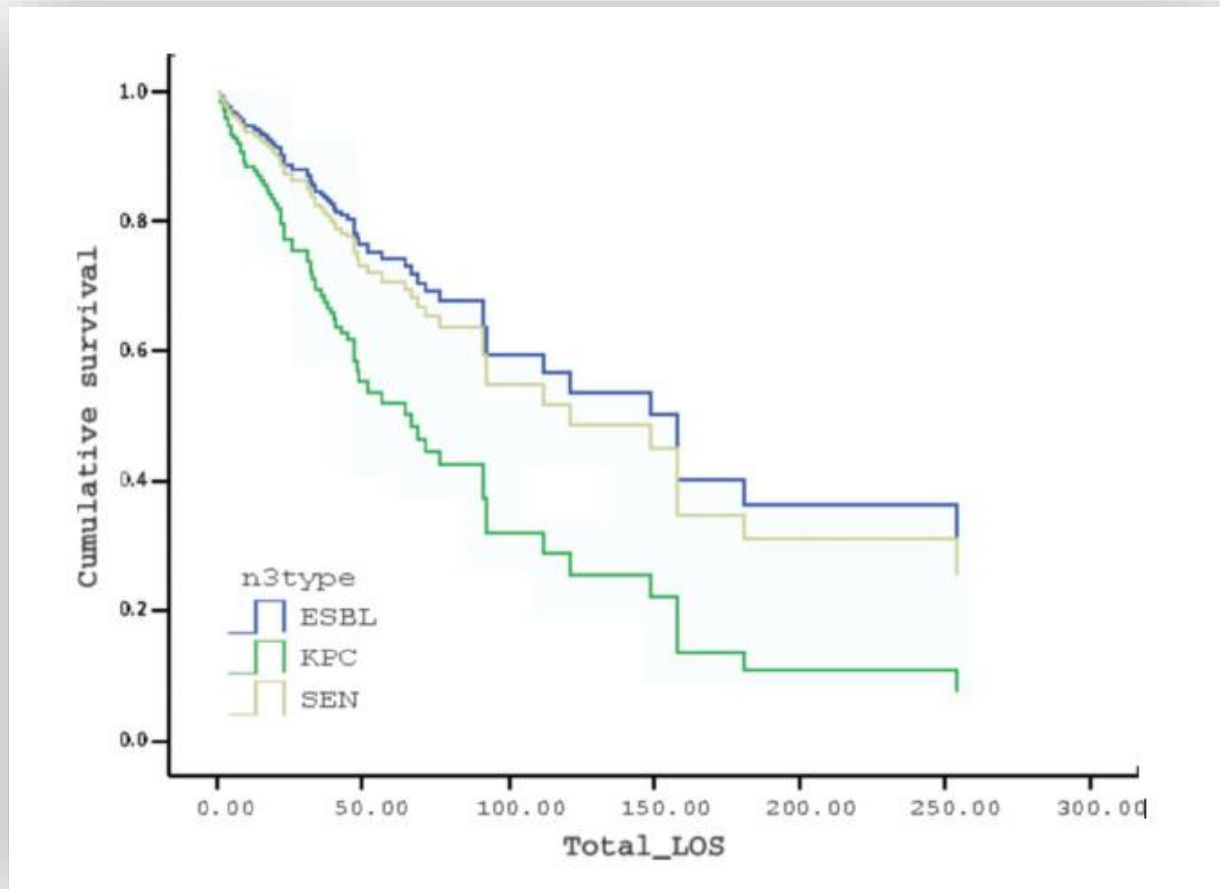
TABLE 4. Independent risk factors for mortality among patients with *Klebsiella pneumoniae* bloodstream infections

Variable	Adjusted OR (95% CI)	p
All cause mortality		
Charlson co-morbidity score	1.3 (1.09–1.47)	0.01
Pitt bacteraemia score	1.86 (1.54–2.25)	<0.001
Carbapenem resistance	8.17 (2.66–25.12)	<0.001
ESBL production	1.69 (0.63–4.5)	0.23
Infection-related mortality		
Charlson co-morbidity score	1.18 (1.97–22.67)	0.02
Pitt bacteraemia score	1.54 ((1.34–1.77)	<0.001
Carbapenem resistance	3.89 (1.34–11.25)	0.01
ESBL production	1.20 (0.43–3.36)	0.72

CI, confidence interval; ESBL, extended-spectrum β -lactamase; OR, odds ratio.

Klebsiella pneumoniae BSIs

Ben-David CMI 2012



Survival adjusted on Pitt bacteremia and Charlson scores

Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study



Marie-Laurence Lambert, Carl Suetens, Anne Savey, Mercedes Palomar, Michael Hiesmayr, Ingrid Morales, Antonella Agodi, Uwe Frank, Karl Mertens, Martin Schumacher, Martin Wolkewitz

Exposure	Hazard ratio for ICU deaths (95% CI)		Excess length of stay in ICU (days)	Hazard ratio for ICU discharge, dead or alive (95% CI)	
	Time-adjusted	Fully adjusted		Time-adjusted	Fully adjusted
<i>Acinetobacter baumannii</i> (ceftazidime sensitive)	4.3 (2.6-7.1)	2.2 (1.3-3.6)	16.6	0.58 (0.42-0.80)	0.65 (0.46-0.92)
<i>Acinetobacter baumannii</i> (ceftazidime resistant)	3.1 (2.2-4.3)	2.2 (1.6-3.0)	6.9	0.82 (0.68-0.99)	0.92 (0.76-1.11)
<i>Acinetobacter baumannii</i> (unknown)	8.7 (7.1-10.6)	3.3 (2.7-4.1)	..	0.72 (0.64-0.82)	0.77 (0.68-0.87)
<i>Escherichia coli</i> (C3G sensitive)	3.4 (2.9-4.1)	1.7 (1.5-2.1)	7.7	0.69 (0.62-0.76)	0.83 (0.75-0.92)
<i>Escherichia coli</i> (C3G resistant)	6.1 (4.1-9.2)	2.5 (1.6-3.8)	6.1	0.71 (0.53-0.95)	0.81 (0.60-1.09)
<i>Pseudomonas aeruginosa</i> (ceftazidime sensitive)	6.1 (5.6-6.8)	2.8 (2.6-3.1)	7.8	0.70 (0.66-0.75)	0.87 (0.82-0.93)
<i>Pseudomonas aeruginosa</i> (ceftazidime resistant)	7.6 (6.4-9.0)	3.5 (2.9-4.2)	8.1	0.70 (0.62-0.78)	0.84 (0.74-0.94)
MSSA	2.7 (2.4-3.1)	1.7 (1.4-1.9)	4.6		
MRSA	4.3 (3.7-5.0)	2.1 (1.8-2.5)	5.2		
All four sensitive microorganisms	4.4 (4.1-4.8)	2.3 (2.1-2.5)	7.2		
All four resistant microorganisms	5.5 (4.9-6.2)	2.8 (2.5-3.1)	6.3		
Ratios of hazard ratios: resistant vs sensitive					
<i>Acinetobacter baumannii</i>	0.7 (0.4-1.3)	1.0 (0.6-1.8)	..		
<i>Escherichia coli</i>	1.8 (1.2-2.8)	1.4 (0.9-2.3)	..		
<i>Pseudomonas aeruginosa</i>	1.2 (1.0-1.5)	1.2 (1.0-1.5)*	..	1.00 (0.88-1.13)	0.96 (0.84-1.09)
<i>Staphylococcus aureus</i>	1.6 (1.3-1.9)	1.3 (1.0-1.6)*	..	1.03 (0.92-1.15)	1.03 (0.92-1.10)
All four microorganisms combined	1.3 (1.1-1.4)	1.2 (1.1-1.4)	..	1.05 (0.97-1.13)	1.05 (0.97-1.13)

P aeruginosa X1.2
S aureus X 1.3
 All four organisms X1.2

Exposed patients are compared with the rest of the cohort. A lower hazard ratio for discharge value (<1) shows a smaller hazard of being discharged and a longer excess length of stay. For the time-adjusted model, the length of stay before infection was implicitly adjusted for. For the fully adjusted model, adjustment was also made for baseline variables (age, sex, simplified acute physiology score II score on admission, type of admission [medical, scheduled surgery, or unscheduled surgery], origin of patients [other ward on same hospital, other ICU, long-term care facility, community], trauma, impaired immunity, antibiotics within 48 h of admission, and number of days with intubation and central venous catheter). ICU=intensive-care unit. C3G= third-generation cephalosporins. MSSA=meticillin-sensitive *Staphylococcus aureus*. MRSA=meticillin-resistant *Staphylococcus aureus*. *p<0.05.

Table 4: Health-care-associated pneumonia: hazard ratios for ICU death and discharge (dead or alive), and excess length of stay

Subdistribution hazard model stratified by center and countries

Excess Mortality and hospital LOS associated with *E. coli* resistant to 3rd-gen cephalosporins BSI

Table 3. Impact of REC or SEC BSI on 30 day mortality: univariate and multivariate logistic regression, and comparison of adjusted effect estimates from both cohorts

Type of analysis	<i>n</i>	OR for effect measure (95% CI)	Effect measure; potential confounders in model
REC versus controls			
univariate	294	7.2 (3.4–15.2)	REC BSI
multivariate	248	4.6 (1.7–12.3)	REC BSI; tracheal tube, central venous catheter, urinary catheter, transfer from another institution, CCI, number of indwelling devices
SEC versus controls			
univariate	2961	2.7 (2.2–3.4)	SEC BSI
multivariate	2494	1.9 (1.4–2.5)	SEC BSI; age, emergency admission, central venous catheter, urinary catheter, transfer from another institution, number of indwelling devices
REC cohort versus SEC cohort			
comparison of adjusted effect estimates		2.5 (0.9–6.8)	third-generation cephalosporin resistance of <i>E. coli</i> BSI

OR, odds ratio.

Clinical impact of Methicillin resistance

Cohort I: MRSA BSI (248) and cohort II MSSA BSI (618).
 In both cohorts : matched for LOS prior to the onset of BSI.

	Outcome	Adjusted estimates for the burden of bloodstream infection and resistance*		
		MRSA bloodstream infection vs no <i>Staphylococcus aureus</i> bloodstream infection OR or SHR (95% CI)	MSSA bloodstream infection vs no <i>S aureus</i> bloodstream infection OR or SHR (95% CI)	Burden of resistance: ratio of ORs and SHRs for MRSA vs MSSA
Time-matched subcohort of patients in hospitals in Europe ²	Mortality 30 days after infection or enrolment	OR 4.4 (2.8-7.0)	OR 2.4 (1.7-3.3)	OR 1.8 (1.04-3.2)
Cohort of patients in intensive-care units in Europe ¹	Mortality in intensive-care unit	SHR 3.3 (2.5-5.2)	SHR 2.1 (1.6-2.6)	SHR 1.6 (1.1-2.3)

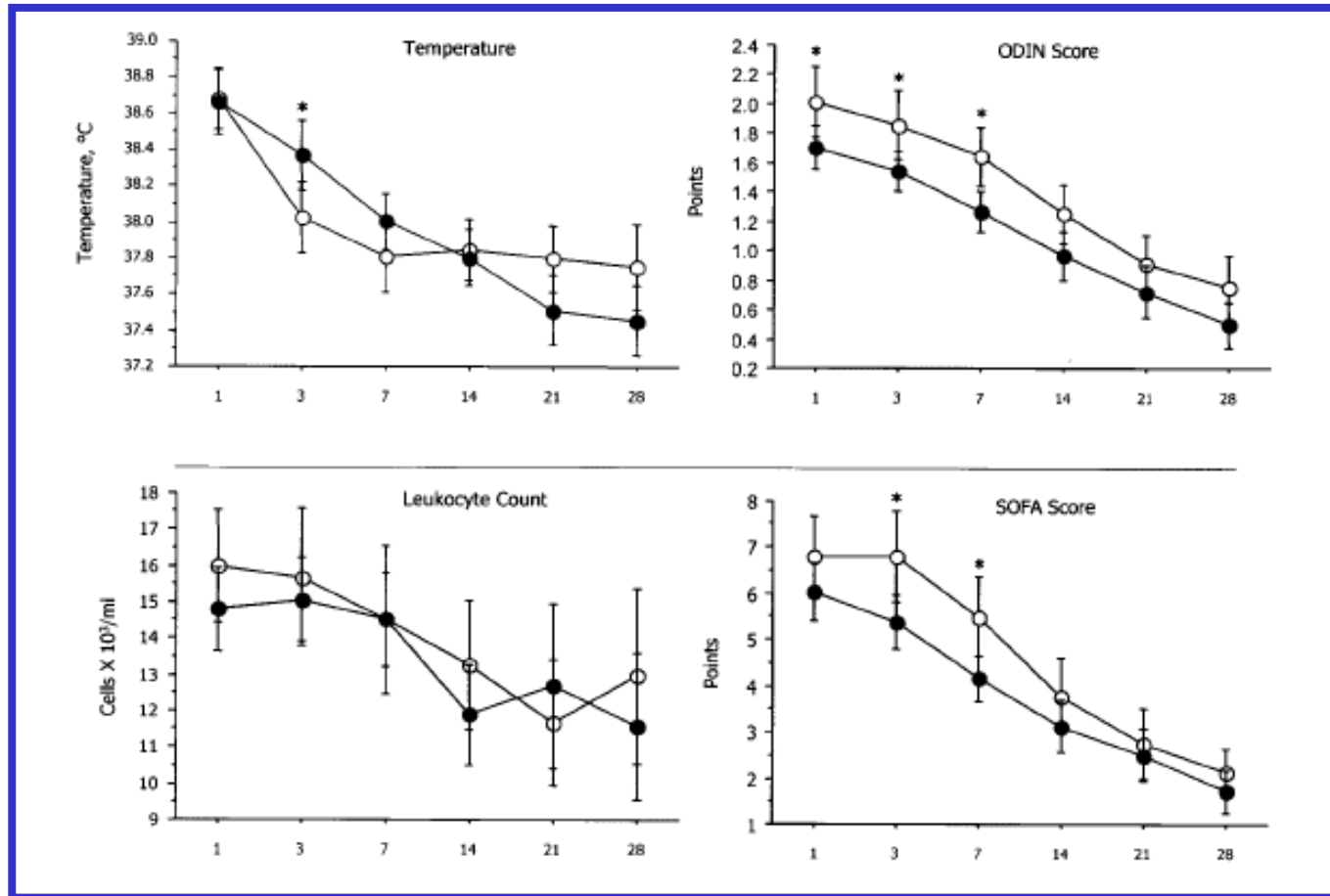
*Factors of adjustment differed between the two studies. MRSA=meticillin-resistant *S aureus*. MSSA=meticillin-susceptible *S aureus*. OR=odds ratio. SHR=subdistribution hazard ratio.

Table: Mortality related to *Staphylococcus aureus* bloodstream infection in two studies with different designs

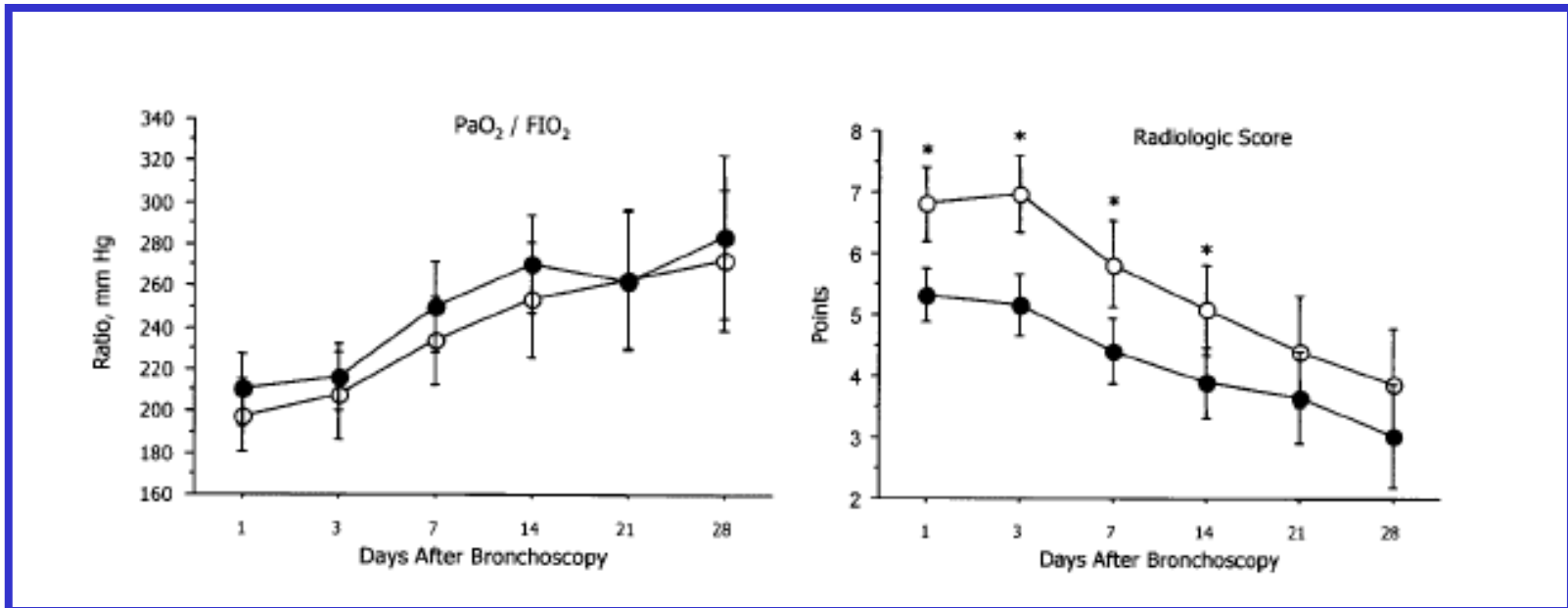
The rate of complications associated with VAP is not different between MRSA and MSSA

	MRSA	MSSA
	N=32	N=54
Septic shock	43%	33%
Acute renal failure	50%	37%
Neurological alteration	22%	17%
Hepatic alteration	13%	11%
Respiratory distress	21%	37%
DIC	3%	2%

No direct impact of methicillin resistance on organ response



No direct impact of methicillin resistance on organ response



Combes et al, AJRCCM 2004

Inappropriate Abx therapy more than resistance alone explained prognosis

4006 episodes of severe sepsis in ICU

	Univariate	Multivariate*
Community-acquired (n=1562)	MRB: Alive 3.4%, Dead 6%	s HR 0.87 (0.54-1.4), 0.56
	IAT: Alive 21% vs Dead 29%	s HR 1.7 (1.4-1.98), <0.0001
Hospital acquired (n= 1432)	MRB: Alive 8% vs Dead 13%	s HR 1.11 (0.82-1.52), 0.49
	IAT Alive 22 vs Dead 29%	s HR 1.35 (1.12-1.92), <0.0001
ICU-acquired n=1012	MRB: Alive 26 vs Dead 32%	s HR 0.98 (0.77-1.22), 0.9
	IAT Alive 46 vs Dead 51%	s HR 1.2 (1.05-1.75), 0.03

•Competing risk models adjusted on species, severity, chronic illnesses

s HR: subdistribution hazard ratio

MRB:multiresistant bacteria

IAT:inappropriate antimicrobial therapy

When appropriately treated, resistance to methicillin did not remain associated with death

Ventilator-associated pneumonia

28-day mortality: OR=1.72 (0.73-4.05) p=0.22

(appropriate treatment only)

Combes et al 2004

ICU death OR=0.82 [0.1-6.95] p=0.85

hospital death OR=0.506 95%CI [0.06-4.13] p=0.52

(appropriately treated subgroup only)

Zahar et al 2005

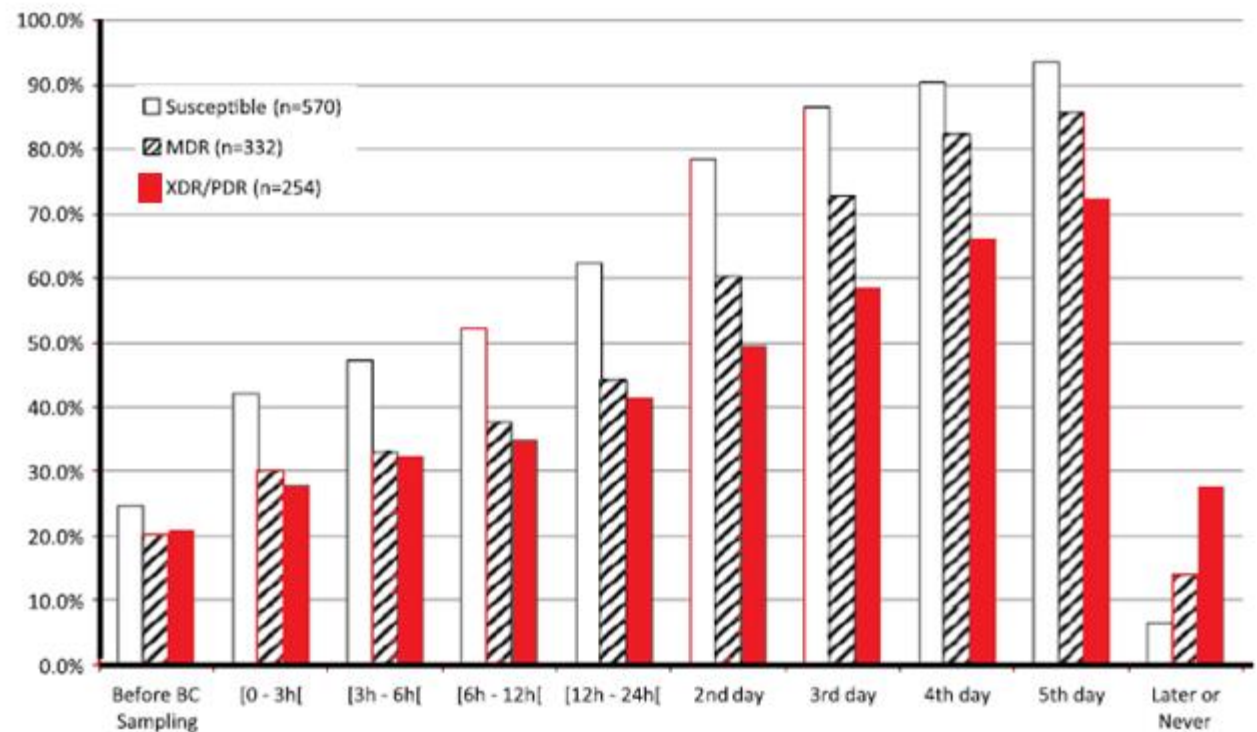
Resistance virulence and fitness..

- EUROBACT study (2010)
- 1156 hospital acquired bacteremia 24 countries, 162 ICUs in Europe
- RF factor of day 28 mortality using a hierarchical logistic model
- Definition of resistance using the new international expert proposal *(Magiorakos et al - Clin Microbiol Infect. 2011 May 7. doi: 10.1111/j.1469-0691.2011.03570.x. [Epub ahead of print])*
 - *Susceptible*
 - *MDR: ≥ 1 agent in 3 or more Abx families*
 - *XDR: ≥ 1 agent all but 2 Abx families*
 - *PDR : all agents in all Abx families*

Alexis Tabah
Despoina Koulenti
Kevin Laupland
Benoit Misset
Jordi Valles
Frederico Bruzzi de Carvalho
José Artur Paiva
Nahit Çakar
Xiaochun Ma
Philippe Eggimann
Massimo Antonelli
Marc J. M. Bonten
Akos Csomos
Wolfgang A. Krueger
Adam Mikstacki
Jeffrey Lipman
Pieter Depuydt
Aurélien Vesin
Maité Garrouste-Orgeas
Jean-Ralph Zahar
Stijn Blot
Jean Carlet
Christian Brun-Buisson
Claude Martin
Jordi Rello
Georges Dimopoulos
Jean-François Timsit

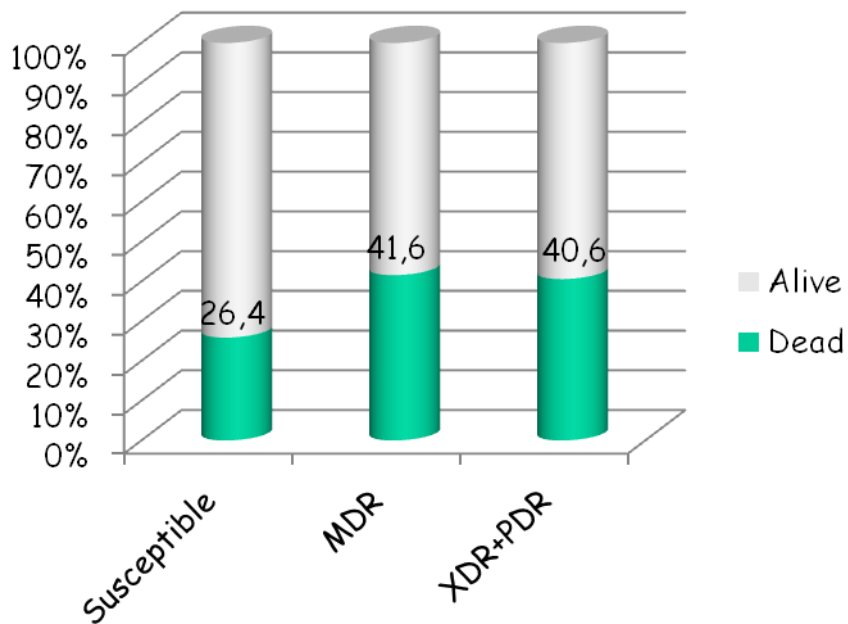
Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study

Intens Care Med 2012 Epub Sept 26th



Decrease in virulence when XDR or PDR?

D28 MORTALITY



Multidrug resistant*
OR 1.51 [1.12 - 2.02] p= 0.006
No adequate treatment*
OR 1.56 [1.04 - 2.35] p= 0.03
(*) Adjusted on chronic illness,
SAPS II, procedures, shock, site
and type of infection

But when the strains become pan-resistant?

111 KPC septic shock - *Falcone et al CMI 2016; 22:444*

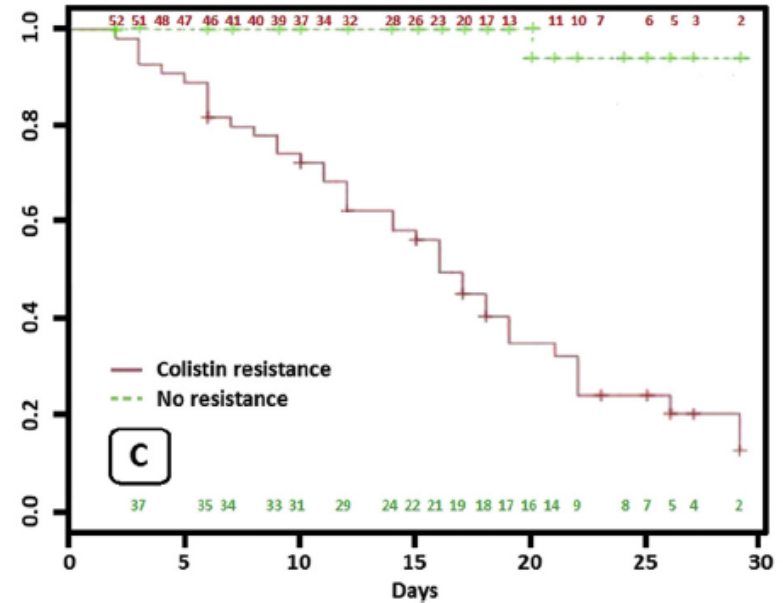
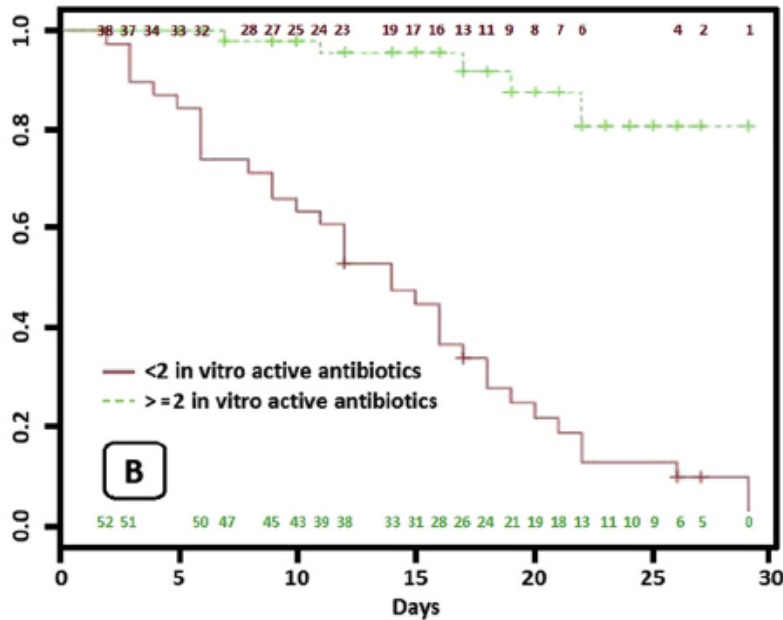


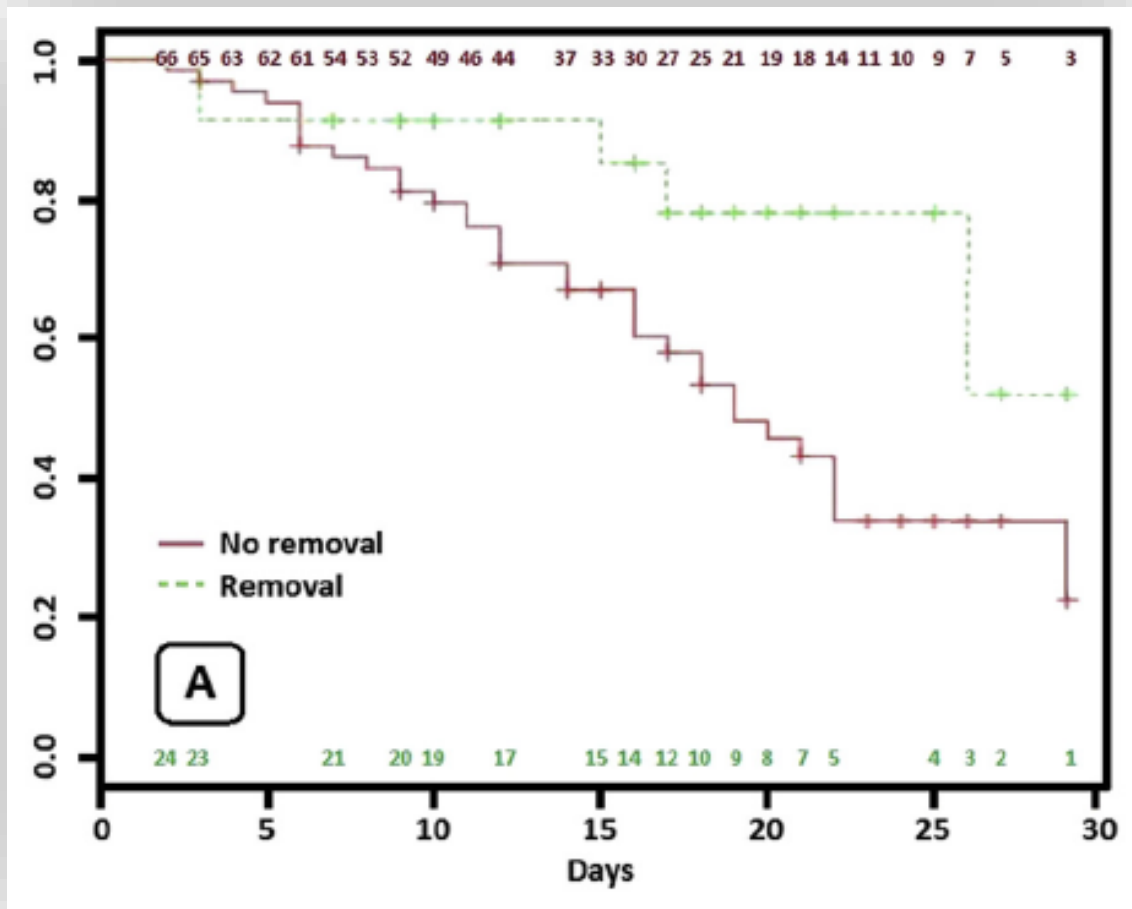
TABLE 3. Cox regression analysis of factors associated with death

Factor	HR	95% CI	p
Colistin-containing antibiotic regimen	0.21	0.05–0.72	<0.001
Two or more <i>in vitro</i> active antibiotics as definitive therapy	0.08	0.02–0.21	<0.001
Control of removable source of infection	0.14	0.04–0.25	<0.001
Colistin-resistant strain	8.09	3.14–11.23	0.001
Intra-abdominal source of infection	2.92	2.11–4.12	0.002

CI, confidence interval; HR, hazard ratio.

In XDR infection control of the source is key

111 KPC septic shock - *Falcone et al CMI 2016; 22:444*



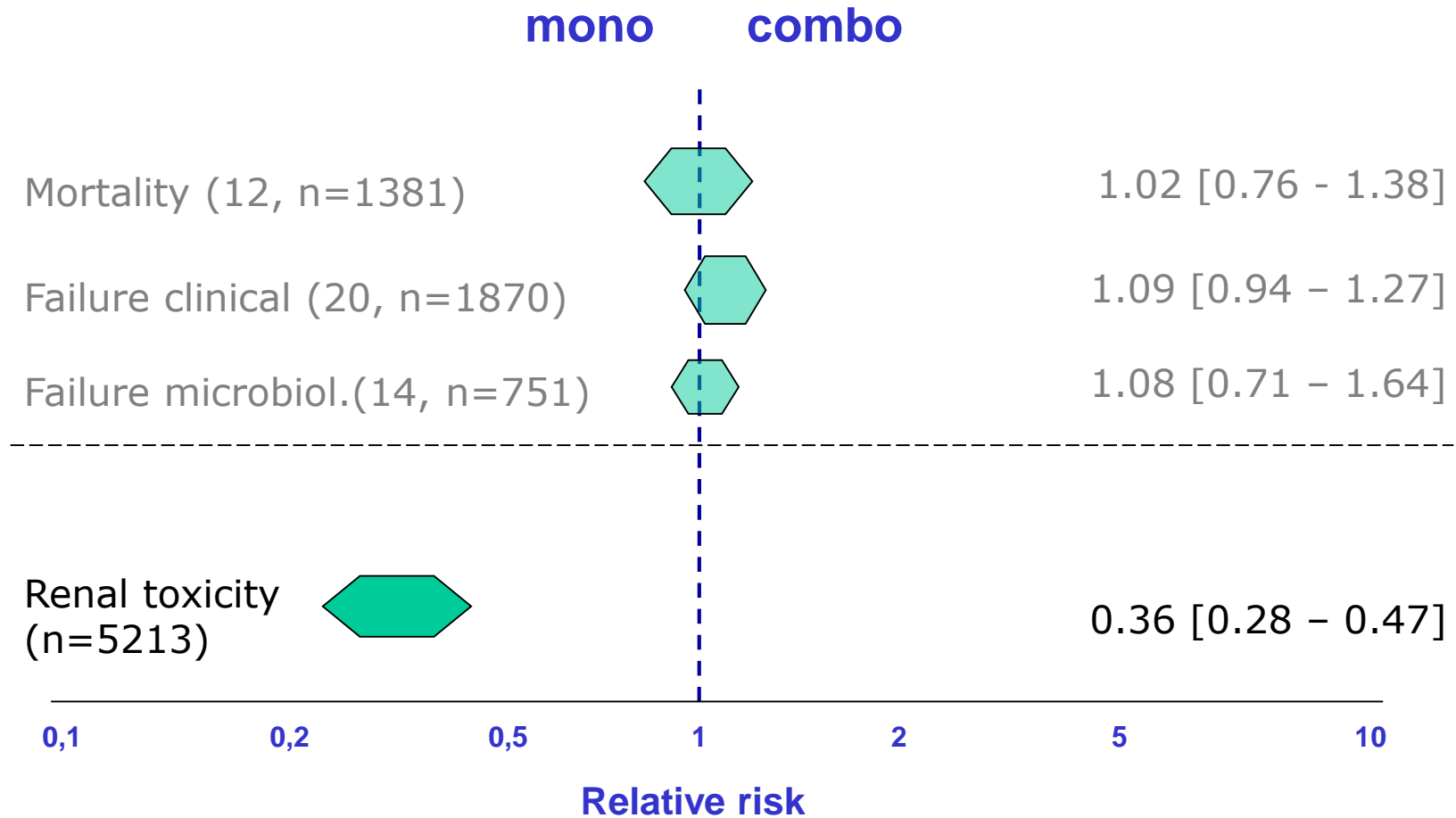
In case of resistance, bi antibiotic therapy with aminoglycosides increase the proportion of adequate antibiotic therapy

4863 episodes de bacteremia with GNB

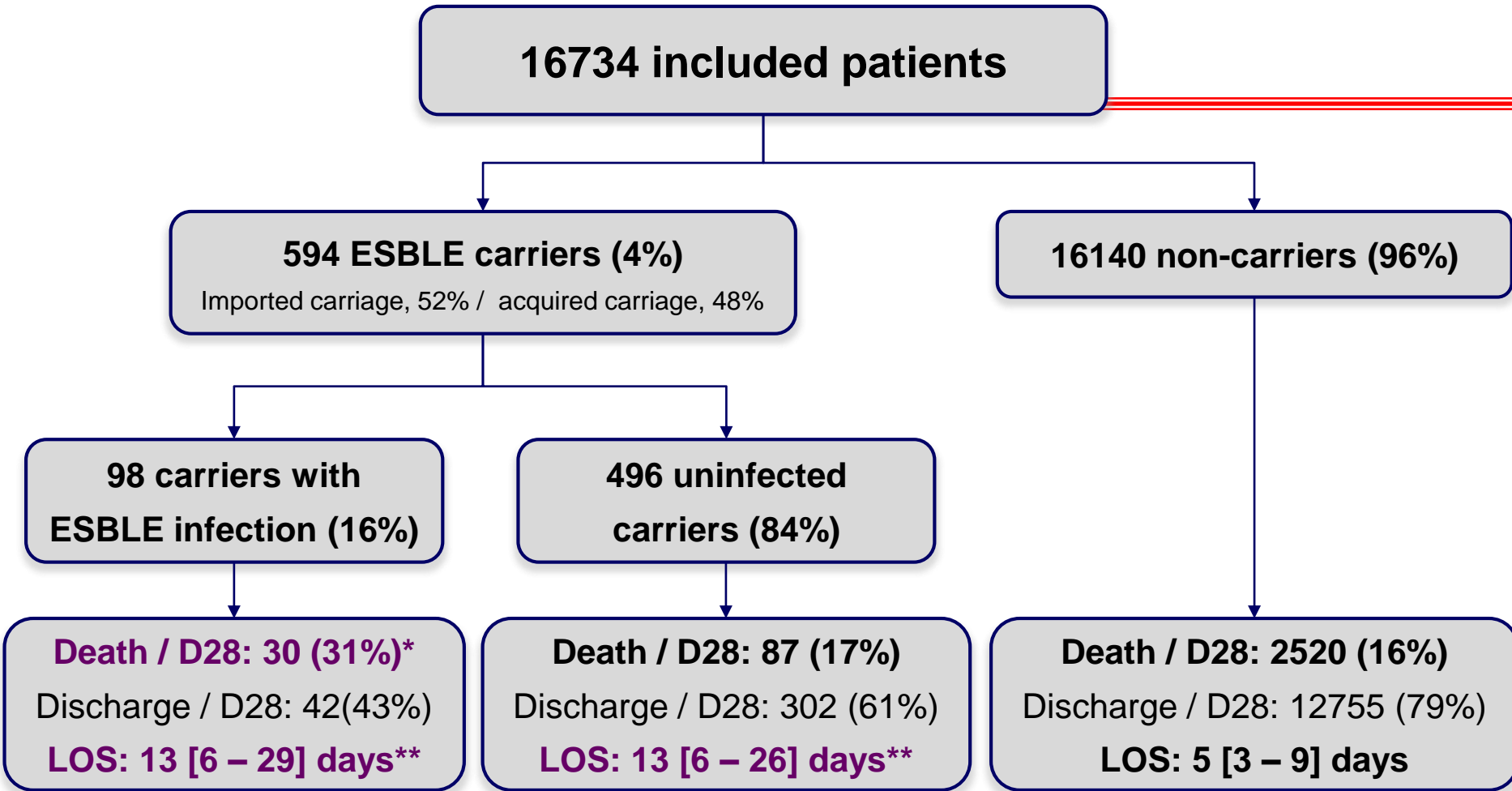
Microorganism	Combination No./total no. (%)	Beta-lactam No./total no. (%)	OR (95% CI)	P
Non-ESBL <i>E. coli</i>	242/248 (98)	2,454/2,489 (99)	0.6 (0.2-1.7)	0.3
ESBL <i>E. coli</i>	21/28 (75)	62/122 (51)	2.9 (1.1-8.2)	0.02
Non-ESBL <i>Klebsiella</i>	62/63 (98)	393/420 (94)	4 (0.7-177)	0.2
ESBL <i>K. pn.</i>	18/20 (90)	38/63 (60)	2 (1.2-4.2)	0.01
<i>P. mirabilis</i>	10/10 (100)	116/118 (98)		1
<i>Salmonella</i> spp.	15/15 (100)	108/109 (99)		1
AmpC organisms	78/82 (95)	258/326 (79)	5.1 (1.8-20)	0.001
<i>P. aeruginosa</i>	133/143 (93)	201/319 (63)	7.8 (3.8-16)	<.0001
Other NF-GNB	24/51 (47)	53/105 (51)	0.9 (0.4-1.8)	0.7
Miscellaneous	18/18 (100)	105/114 (92)		0.4

Combo with aminoglycosides is associated with renal failure

Same beta-lactamin



Impact of ESBLE colonization and infection on mortality, LOS and antimicrobial use



**Delayed adequate antimicrobial therapy (≥ 24 hours)
in 58 patients (59%) with a first ESBLE infection**

Colonization and infection with extended-spectrum β -lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure?

François Barbier¹, Cécile Pommier², Wafa Essaied², Maité Garrouste-Orgeas³, Carole Schwebel⁴, Stéphane Ruckly⁵, Anne-Sylvie Dumenil⁶, Virginie Lemiale⁷, Bruno Mourvillier⁸, Christophe Clec'h⁹, Michaël Darmon¹⁰, Virginie Laurent¹¹, Guillaume Marcotte¹², Jean-Christophe Lucet^{2,13}, Bertrand Souweine¹⁴, Jean-Ralph Zahar¹⁵ and Jean-François Timsit^{2,8*} on behalf of the OUTCOMEREA Study Group†

	Death in the ICU at D28			Discharge alive at D28		
	aCSHR	95% CI	<i>p</i> value	aCSHR	95% CI	<i>p</i> value
No carriage	1	-	-	1	-	-
ESBLE carriage without infection	0.91	0.72 - 1.14	0.39	0.62	0.55 - 0.70	<0.0001
ESBLE infection	1.82	1.23 - 2.70	0.003	0.56	0.43 - 0.73	<0.0001

aCSHR, adjusted cause-specific hazard ratio; 95% CI, 95% confidence interval

Adjustment on baseline characteristics (chronic diseases, admission type, SAPS II and organ failures at admission) and time-dependent variables (SOFA score and end-of-life decisions)

Colonization and infection with extended-spectrum β -lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure?

François Barbier¹, Cécile Pommier², Wafa Essaied², Maité Garrouste-Orgeas³, Carole Schwebel⁴, Stéphane Ruckly⁵, Anne-Sylvie Dumenil⁶, Virginie Lemiale⁷, Bruno Mourvillier⁸, Christophe Clec'h⁹, Michaël Darmon¹⁰, Virginie Laurent¹¹, Guillaume Marcotte¹², Jean-Christophe Lucet^{2,13}, Bertrand Souweine¹⁴, Jean-Ralph Zahar¹⁵ and Jean-François Timsit^{2,8*} on behalf of the OUTCOMEREA Study Group†

	Death in the ICU at D28			Discharge alive at D28		
	aCSHR	95% CI	<i>p</i> value	aCSHR	95% CI	<i>p</i> value
No carriage	1	-	-	1	-	-
ESBLE carriage without infection	0.91	0.72 - 1.14	0.39	0.62	0.55 - 0.70	<0.0001
ESBLE infection	1.82	1.23 - 2.70	0.003	0.56	0.43 - 0.73	<0.0001

aCSHR, adjusted cause-specific hazard ratio; 95% CI, 95% confidence interval

Increased the risk of death and decreased the hazard of discharge

OUTCOME REA

Colonization and infection with extended-spectrum β -lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure?

François Barbier¹, Cécile Pommier², Wafa Essaied², Maité Garrouste-Orgeas³, Carole Schwebel⁴, Stéphane Ruckly⁵, Anne-Sylvie Dumenil⁶, Virginie Lemiale⁷, Bruno Mourvillier⁸, Christophe Clec'h⁹, Michaël Darmon¹⁰, Virginie Laurent¹¹, Guillaume Marcotte¹², Jean-Christophe Lucet^{2,13}, Bertrand Souweine¹⁴, Jean-Ralph Zahar¹⁵ and Jean-François Timsit^{2,8*} on behalf of the OUTCOMEREA Study Group†

	Death in the ICU at D28			Discharge alive at D28		
	aCSHR	95% CI	<i>p</i> value	aCSHR	95% CI	<i>p</i> value
No carriage	1	-	-	1	-	-
ESBLE carriage without infection	0.91	0.72 - 1.14	0.39	0.62	0.55 - 0.70	<0.0001
ESBLE infection	1.82	1.23 - 2.70	0.003	0.56	0.43 - 0.73	<0.0001

aCSHR, adjusted cause-specific hazard ratio; 95% CI, 95% confidence interval

No impact on the hazard of death but decreased the hazard of discharge

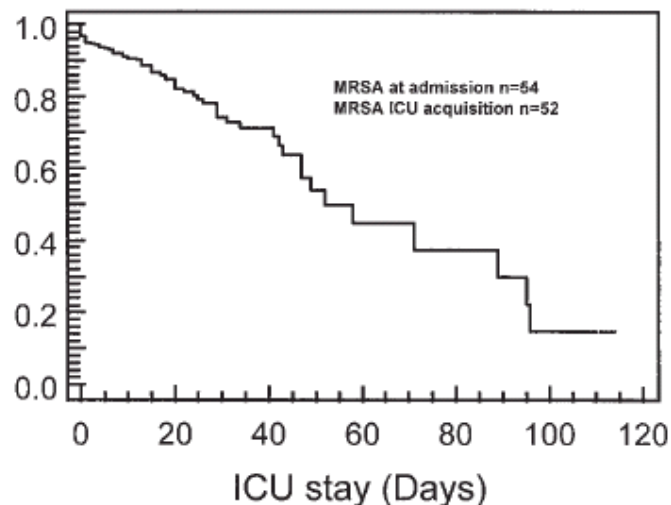
Colonization and infection with extended-spectrum β -lactamase-producing Enterobacteriaceae in ICU patients: what impact on outcomes and carbapenem exposure?

François Barbier¹, Cécile Pommier², Wafa Essaied², Maité Garrouste-Orgeas³, Carole Schwebel⁴, Stéphane Ruckly⁵, Anne-Sylvie Dumenil⁶, Virginie Lemiale⁷, Bruno Mourvillier⁸, Christophe Clec'h⁹, Michaël Darmon¹⁰, Virginie Laurent¹¹, Guillaume Marcotte¹², Jean-Christophe Lucet^{2,13}, Bertrand Souweine¹⁴, Jean-Ralph Zahar¹⁵ and Jean-François Timsit^{2,8*} on behalf of the OUTCOMEREA Study Group†

Antibiotic classes	Nb of days on antimicrobials pour 1000 patient-days			<i>p</i>
	No colonization	Colonization Without infection	Infection	
Carbapenems	69	241	627	<0,0001
BL-BLI	220	103	123	<0,0001
Fluoroquinolones	114	87	108	0,89

ESBL colonization associated with a 4-fold increase in carbapenem consumption in the absence of proven ESBL infection

Colonization with MRSA without infection increase antibiotic use



1044 patients
42 S. aureus infections/ 35
patients
(32 MRSA/10 MSSA)

1/ MRSA colonization independently associated with *S. aureus* infections

Hazard ratio=3.84, $p<0.0001$

2/ Glycopeptides consumption (Nb of days in use) is 3.3 fold more important in colonized NON infected patients than in NON colonized NON infected patients

117‰ vs 35.6 ‰ days, $p<0.001$

Increase of vancomycin level is associated with success rate in MRSA infections (95 patients, 77% pneumonias)

Target: Population Through > 15 mg/l & Through $\geq \text{MIC} \times 4$

	MIC<2	MIC=2	p
Success	85%	62%	0.02
Néphrotoxicity	0	12%	<0.05
Mortality	10%	24%	0.16

But also with renal toxicity...

Isolation could be dangerous..

- Decrease of care
 - « It is hard to go inside the room »...
 - 2-fold decrease of visits
 - >2-fold decrease quality of survey and care
 - 2-fold more iatrogenic events

KB Kirkland et al - Lancet 1999; 354 : 1177-1178

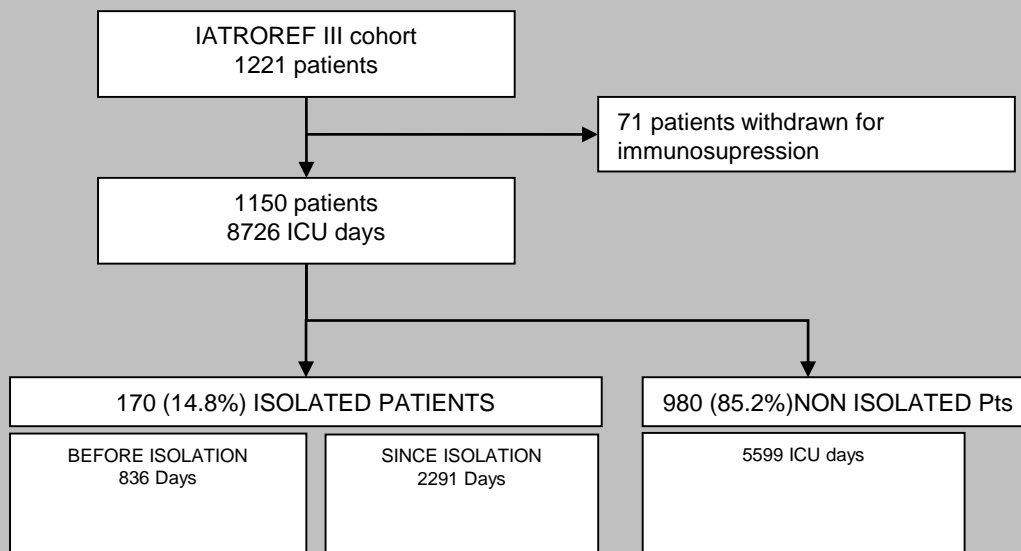
Evans HL et al - Surgery 2003

Stelfax et al - JAMA. 2003;290:1899-1905
- Transfer into hospital ward more difficult (single room)
 - Increase in the duration of stay
 - Increase of colonization pressure
- Increase of anxiety and delirium in isolated patients
- Cost of isolation \$3191 per case *Conterno LO et al - JHI 2007 65:354*
Abad C et al - J hospit infect 2010; 97-102

Contact isolation: Impact in ICU patients

OUTCOME REA

- Post hoc analysis of the Iatroref study (2 ICUs)
- Prospective follow up of targeted medical errors and nosocomial infections
- 1150 immunocompetent patients/ 170 contact isolation



Impact of contact isolation on medical errors

Adverse event	Non isolated patients 980 (100)	Isolated patients 170 (100)	SHR [95% CI]	P\$	SHR [95% CI]	P£
Accidental removal of endotracheal tube or catheter	41 / 784 (6.5)	14 / 148 (9.5)	1.2 [0.6 – 2.5]	0.6	1.3 [0.6 – 2.7]	0.5
Anti coagulant prescription error	66 / 980 (6.7)	23 / 170 (13.5)	2.1 [1.2 – 3.5]	0.007	1.7 [1.0 – 2.9]	0.04
Anti coagulant administration error	31 / 705 (4.4)	12 / 148 (8.1)	1.3 [0.6 – 2.9]	0.5	1.0 [0.4 – 2.3]	0.9
Acoag. administration or prescription error	88 / 705 (12.5)	32 / 148 (21.6)	1.8 [1.1 – 2.8]	0.01	1.5 [0.9 – 2.4]	0.08
Phlebitis / pulmonary embolism	26 / 980 (2.7)	15 / 170 (8.8)	2.8 [1.4 – 5.8]	0.004	1.9 [1.0 – 4.0]	0.08
Hemorrhage						0.2
Packed RBCs administered						0.19
Insulin administration error						0.3
Hypoglycemia						0.01
Hyperglycemia						0.004
Hypernatremia						0.7
VAP	64 / 497 (12.9)	50 / 125 (40)	1.2 [0.7 – 2.0]	0.5	1.2 [0.7 – 1.9]	0.5
VAP (Sensitive isolates)	56 / 497 (11.3)	32 / 125 (25.6)	1.1 [0.6 – 1.9]	0.8	1.1 [0.6 – 1.9]	0.9
VAP (Resistant isolates)	16 / 497 (3.2)	29 / 125 (23.2)	2.2 [1.4 – 3.4]	0.0005	2.1 [1.3 – 3.2]	0.001

Anticoagulant prescription error sHR=1.7, p=0.04

DVT/PE

sHR=1.9, p=0.08

Hypoglycaemia

sHR= 1.5, p=0.01

Hyperglycaemia

sHR=1.5, p=0.004

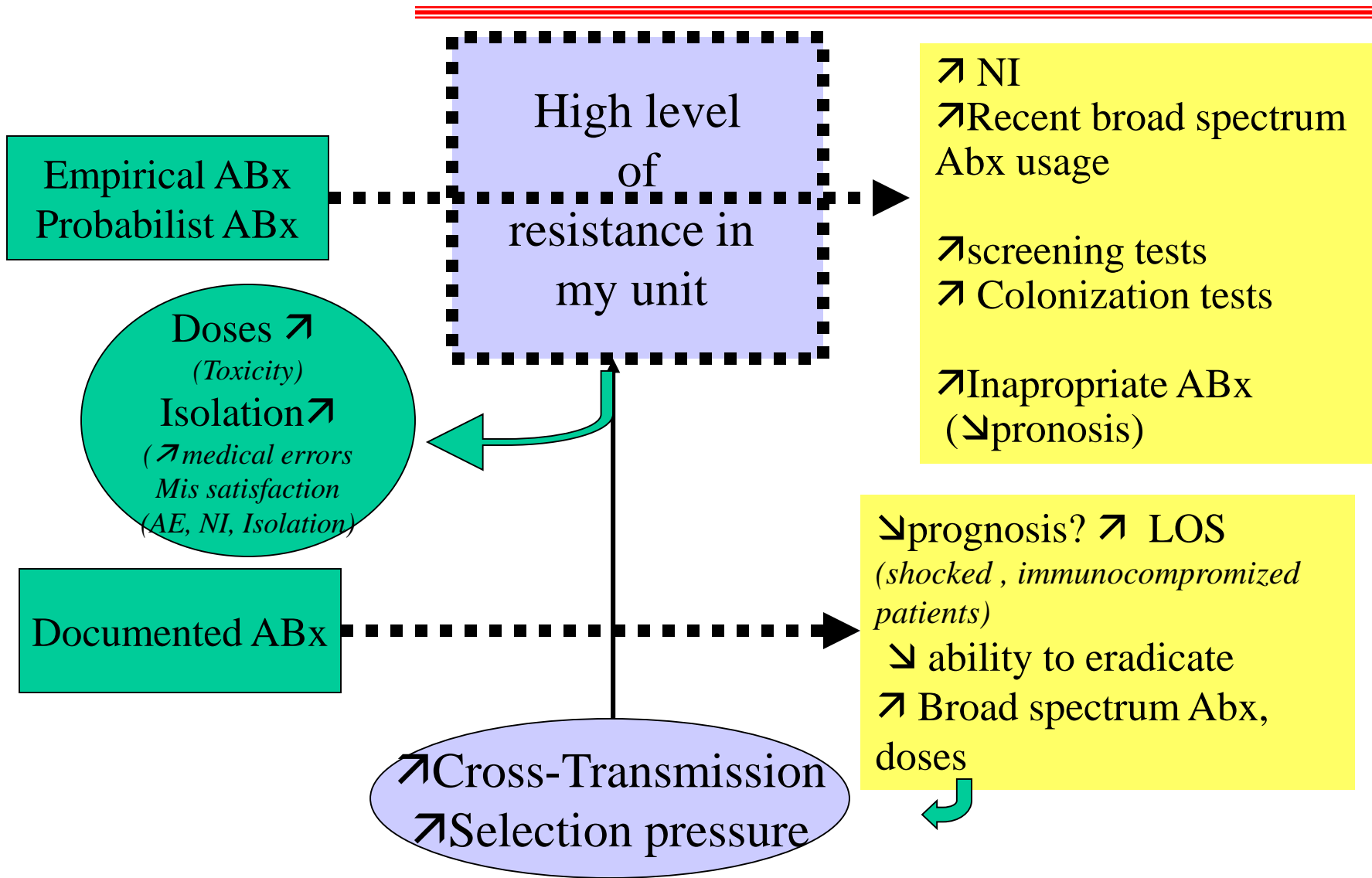
VAP due to resistant isolates

sHR=2.1, p=0.001

\$ Subdistribution hazard model with center stratification

£ Subdistribution hazard model with center stratification and adjustment on risk factors of adverse event

Consequences of bacterial resistance a vicious circle



Clinical impact: To conclude

Patients

Mortality

DIRECT:

↑ Inadequacy of Abx

NO available treatment

INDIRECT:

Isolation

Delay in other diagnosis

Adverse events

Other patients

Colonization pressure

MDR/PDR nosocomial infections

Inadequate care of OTHER PATIENTS

Unit

workload

nb of exams

Insatisfaction, BOS, conflicts

Cost (nurses, Abx...)

And further consequences for Hospital, healthcare policies....