Conséquences de la résistance : L'ANTIBIOTHERAPIE DE RECOURS

Benoît SCHLEMMER

Hôpital Saint-Louis

Université Paris-7 Denis Diderot

Recours = dernier moyen efficace…

Grand Robert de la Langue française, 2e éd., 2001

- Réduction des possibilités thérapeutiques
- Avant l'impasse…!!
- Recours → réserve :

La dernière cartouche …?!

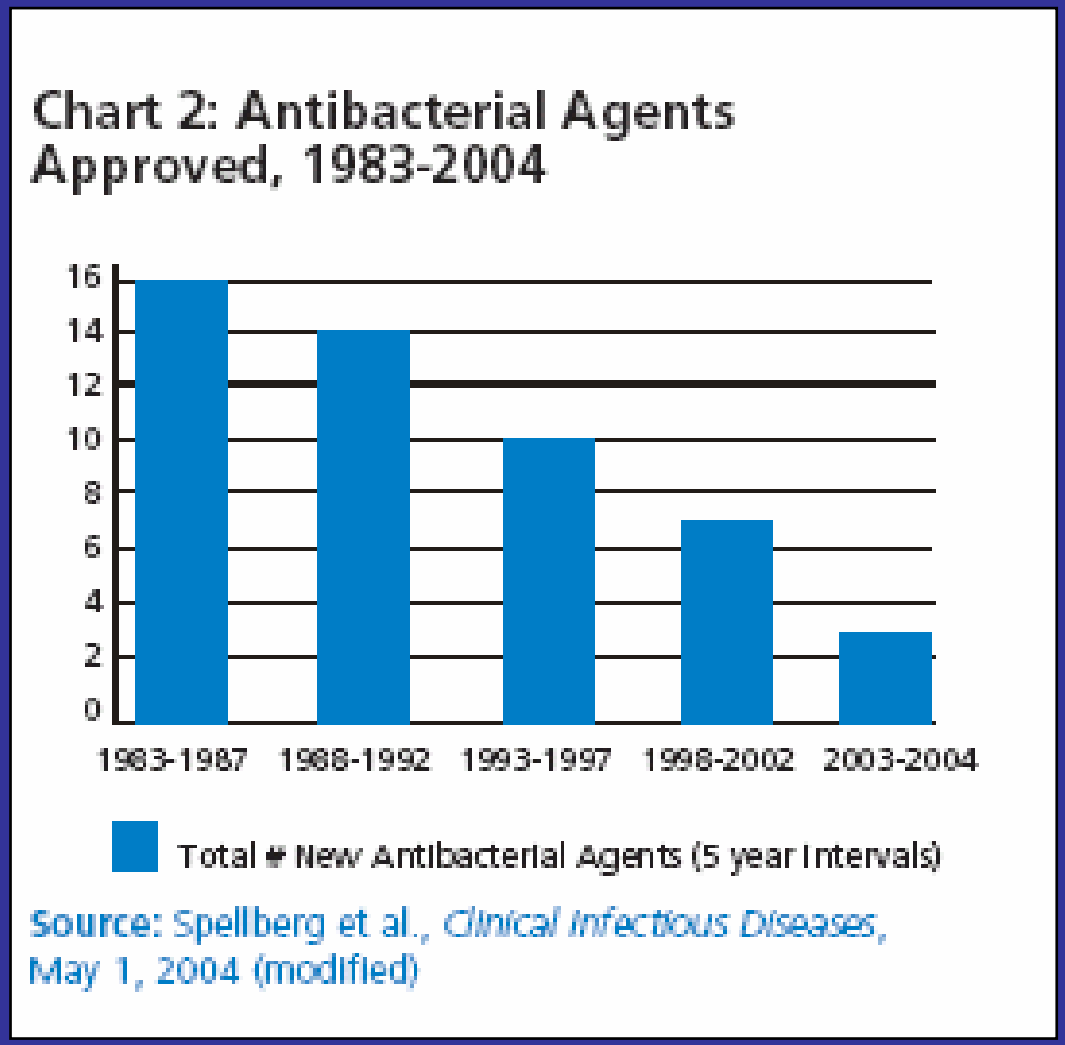
"Allons, faites donner la garde" cria-t-il…
…La garde impériale entra dans la fournaise.

V. Hugo, l'Expiation, Les Châtiments V

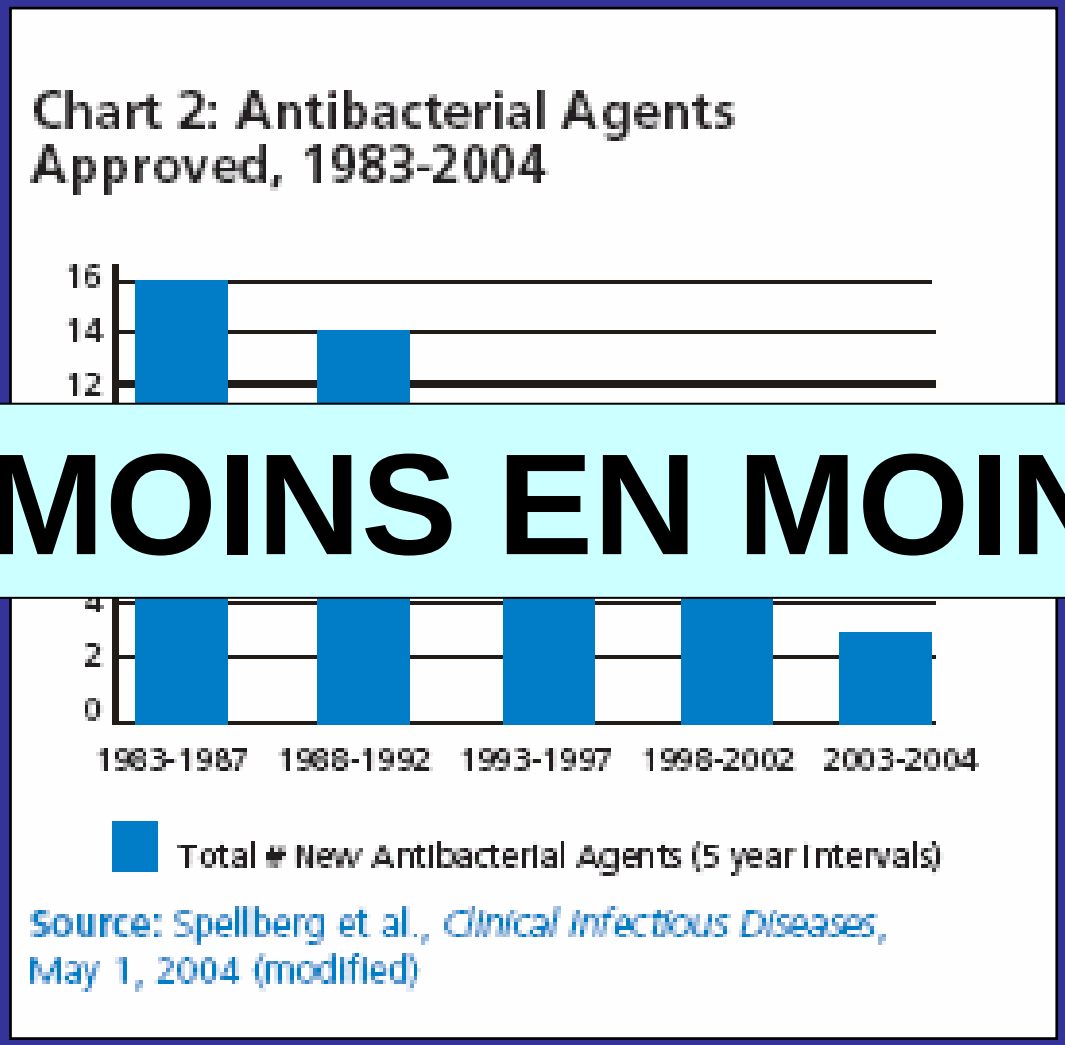
Trois remarques

1. Nouveaux produits : produits de réserve ?
2. Antibiothérapie dirigée
3. Antibiothérapie probabiliste

Nouveaux antibiotiques



Nouveaux antibiotiques



DE MOINS EN MOINS !!

NOUVEAUX ANTIBIOTIQUES

- Anti-Gram +
  - Oxazolidinones : linézolide (Zyvoxid)
  - Daptomycine (Cubicin)
- Anti-Gram -
- Spectre large
  - Tigécycline (Tigacyl)
  - Ceftobiprole

QUELLE ACTIVITE ?

Microbiologique ? Clinique ?

Ceftobiprol medocaril: CMI $_{90}$ vs. Gram +

	Ceftobi	Cefotax	Cefepime	Merop	Vanco
MSSA	1	4	8	0.12	2
MRSA	2	>64	>32	>32	2
MRSE	2	>64	>32	>32	4
S.pyogenes	0.06	0.12	0.12	0.12	1
S.pneu Ps	0.03	0.06	0.06	0.03	1
S.pneu Pr	2	4	4	2	0.5
E.faecalis	4	>32	>32	32	>32
E.faecium As	8	>32	>32	>32	>32
E.faecium Ar	32	>32	>32	>32	>32

Ceftobiprol medocaril: CMI $_{90}$ vs. Gram -

	Ceftobi	Cefotax	Cefepime	Cefta	Merop
E.coli	0.06	0.12	0.06		0.06
E.coli βlse+	>32	32	8		0.06
Klebs	0.25	<0.06	0.25		<0.06
Klebs βlse+	>32	64	16		0.25
Citro	8	64	2		0.25
Enter cloacae	8	>64	4		0.25
Acineto	>64	>64	32	>64	16
P.a cefta-S	16	>64	16	8	2
P.a cefta-R	>64	>64	32	>64	16

Interrogations

- Spectre; activité sur souches R
- Pharmacodynamie
  - Produits bactériostatiques (linézolide, tigécycline)
  - Concentrations sériques et tissulaires variables
  - Inconnues PK/PD
  - Associations antibiotiques
- Indications accordées (évaluées)…, et leurs limites !
  - Espèces bactériennes "à problèmes"
  - Sévérité des infections

The Efficacy and Safety of Tigecycline for the Treatment of Complicated Intra-Abdominal Infections: Analysis of Pooled Clinical Trial Data

Babinchak et al., CID 2005

Table 1. Demographic and baseline medical characteristics of the pooled microbiologic modified intent-to-treat population with complicated intra-abdominal infections.

Characteristic	Tigecycline (*n* = 631)	Imipenem-cilastatin (*n* = 631)
Age, mean ± SD, years	47.1 ± 18.6	46.8 ± 18.2
APACHE II score, mean	6.3	6.0
Primary intra-abdominal diagnosis, no. (%) of patients		
Complicated appendicitis	319 (50.6)	307 (48.7)
Complicated cholecystitis	81 (12.8)	95 (15.1)
Intra-abdominal abscess	68 (10.8)	58 (9.2)
Perforation of intestine	67 (10.6)	59 (9.4)
Complicated diverticulitis	39 (6.2)	49 (7.8)
Gastric/duodenal perforation	33 (5.2)	36 (5.7)
Peritonitis	21 (3.3)	22 (3.5)
Other[a]	3 (0.5)	5 (0.8)

Activity of Tigecycline (GAR-936) against *Acinetobacter baumannii* Strains, Including Those Resistant to Imipenem

María Eugenia Pachón-Ibáñez,[1]* Manuel Enrique Jiménez-Mejías,[1] Cristina Pichardo,[1] Ana Cristina Llanos,[2] and Jerónimo Pachón[1]

AAC 2004

TABLE 1. Susceptibilities of 49 *A. baumannii* strains to imipenem and tigecycline

Drug	MIC (μg/ml)[a]			MBC (μg/ml)[b]			% of susceptibility[c]		
	Range	50%	90%	Range	50%	90%	S	I	R
Imipenem	1–128	32	128	1–128	32	128	20	2	78
Tigecycline	1–4	2	2	2–>8	8	>8	92	8	0

Pas de bactéricidie de la tigécycline sur les souches testées

A suivre : **DX-619**

FQ pas comme les autres sur ***S.aureus.***

- CMI 90 SARM : 1; SERM : 0.125
- CMI 90 SARM Q-s Cipro: 0.5 DX-619: 0.008
- CMI 90 SARM Q-r. Cipro: >32, Moxi: 16, DX-619: 1

- Intéressante en termes d'efficacité
- Active sur DNA gyrase ET topoisomérase
- Très résistante aux résistances

- … et de toxicité?

AAC, 2005, 49, 5051 et AAC, 2005, 49, 3325

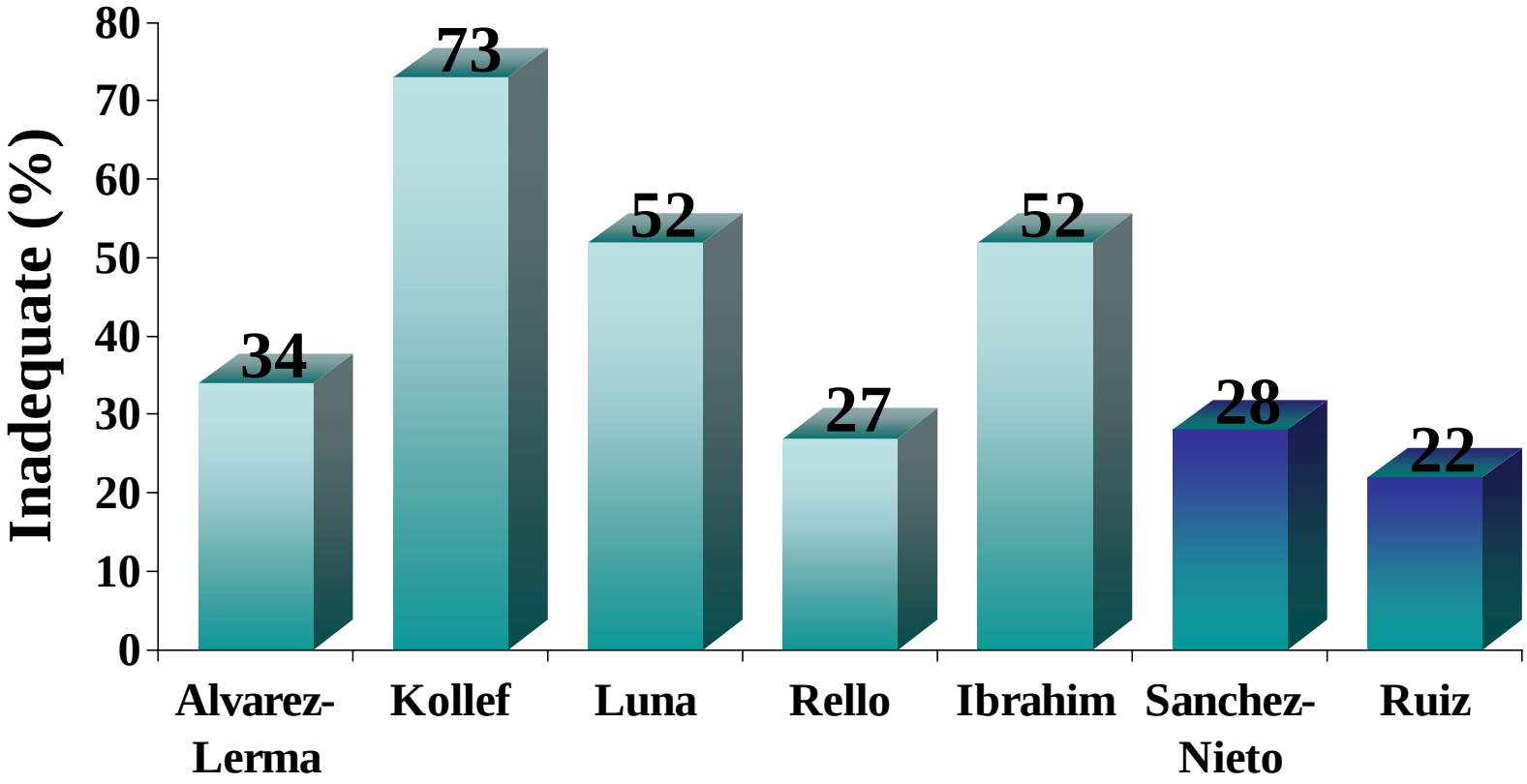
NOUVEAUX ANTIBIOTIQUES

Produits de réserve

ou

Réserves sur produits ???

Inadequate Initial Antimicrobial Therapy (VAP)



Association between Fluoroquinolone Resistance and Mortality in *Escherichia coli* and *Klebsiella pneumoniae* Infections: The Role of Inadequate Empirical Antimicrobial Therapy

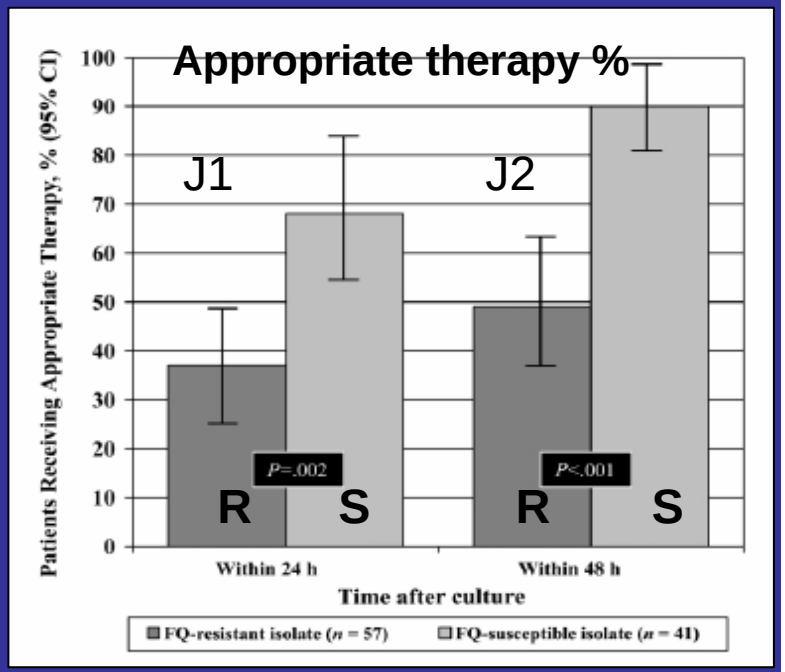
Lautenbach E et al., CID 2005; 41: 923-29

Table 2. Results of a multivariable analysis performed to evaluate the associated with fluoroquinolone (FQ) resistance and mortality in *Escherichia coli* and *Klebsiella pneumoniae* infections.

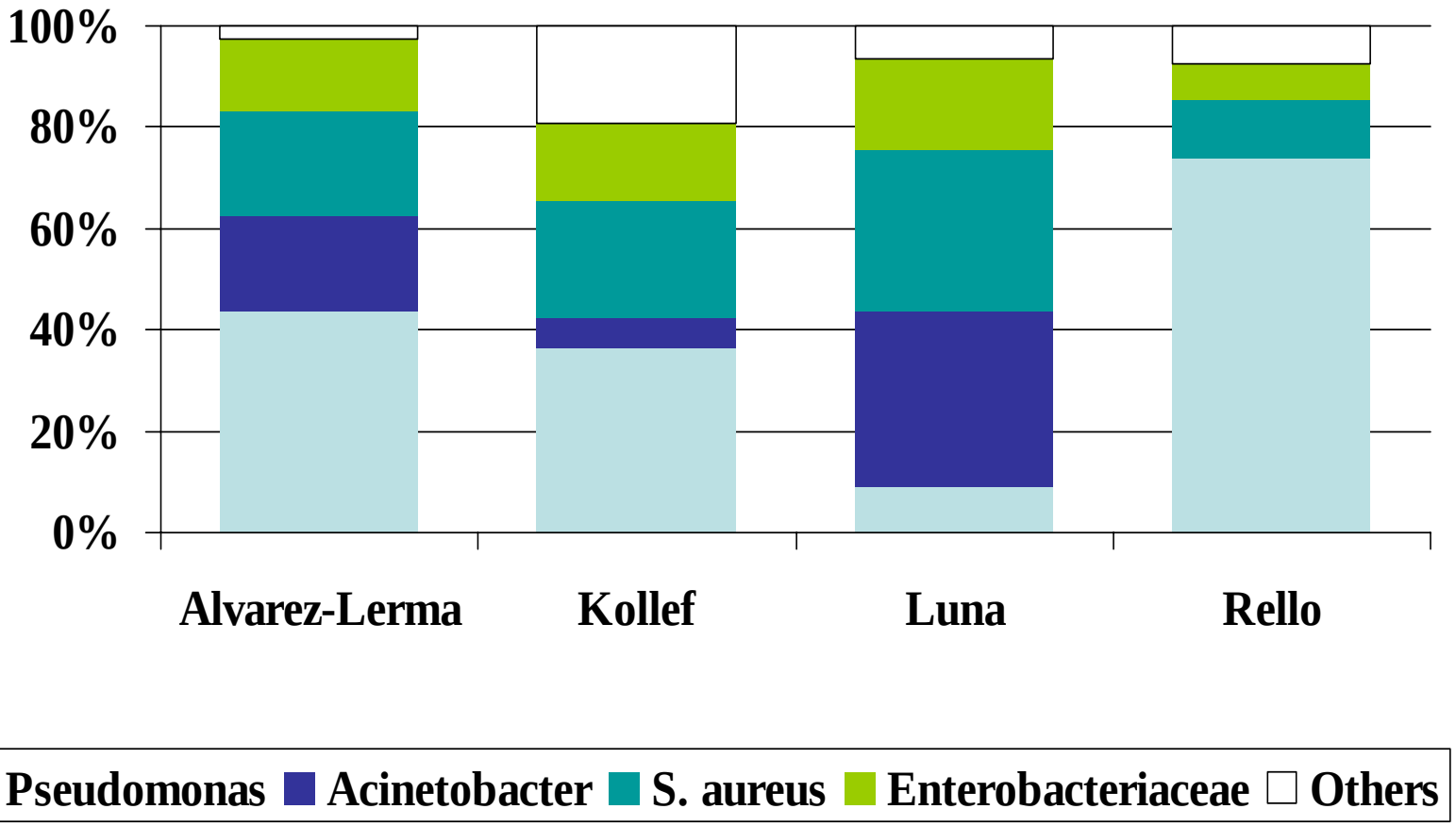
Variable	Adjusted OR (95% CI)	*P*
Infection with FQ-resistant isolate	4.41 (1.03–18.81)	.04
Intensive care unit stay at time of infection	5.50 (1.69–17.88)	.005
APACHE II score[a]	1.14 (1.03–1.26)	.008
African-American race	0.41 (0.14–1.27)	.12

NOTE. All variables included in the final multivariable model are shown.

[a] OR reflects the odds associated with each 1-point increase in the APACHE II score.



Pathogens Associated with Inadequate Initial Therapy



Identifying Groups at High Risk for Carriage of Antibiotic-Resistant Bacteria

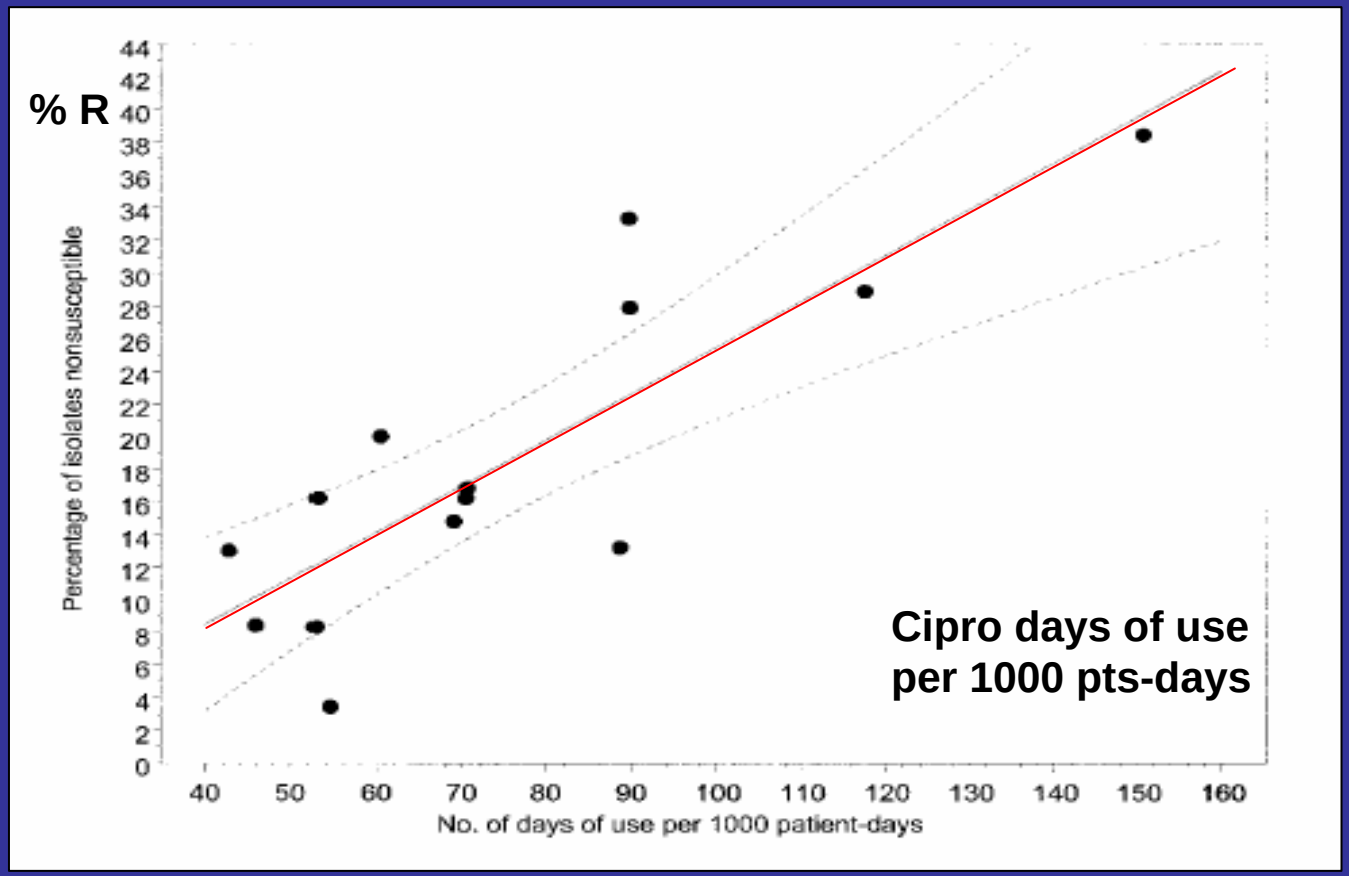
Jon P. Furuno, PhD; Jessina C. McGregor, PhD; Anthony D. Harris, MD, MPH; Judith A. Johnson, PhD; Jennifer K. Johnson, PhD; Patricia Langenberg, PhD; Richard A. Venezia, PhD; Joseph Finkelstein, MD; David L. Smith, PhD; Sandra M. Strauss, BS, M(ASCP); Eli N. Perencevich, MD, MS

Conclusion: Patients with a self-reported previous admission within 1 year may represent a high-risk group for colonization by methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci at hospital admission and should be considered for targeted active surveillance culturing.

Arch Intern Med. 2006;166:580-585

Hospital-Level Rates of Fluoroquinolone Use and the Risk of Hospital-Acquired Infection with Ciprofloxacin-Nonsusceptible *Pseudomonas aeruginosa*

Thomas Ray G et al., CID 2005; 41: 441-9



Ventilator-Associated Pneumonia caused by potentially drug-resistant bacteria

	MV <7d		MV> 7d	
	AB - (n=22)	AB + (n=12)	AB – (n=17)	AB+ (n=84)
Total bacteria	41	20	32	152
P.aeruginosa	0	4 (20%)	2 (6%)	33 (22%)
Acinetobacter, S. maltophilia	0	1 (5%)	1 (3%)	26 (17%)
MRSA	0	1 (5%)	1 (3%)	30 (20%)
Total MR organisms	0	6 (30%)	4 (12%)	89 (59%)
Enterob.	10 (24%)	4 (20%)	28 (87%)	63 (41%)
S.pneumo	3 (7%)	0	0	0
Haemophilus	8 (19%)	2 (10%)	1	4 (3%)
MSSA	6 (15%)	0	7 (22%)	7 (5%)

Trouillet et al, *AJRCCM 1998; 157: 631-39*

Antibiothérapie dirigée

IMPORTANCE DU DIAGNOSTIC

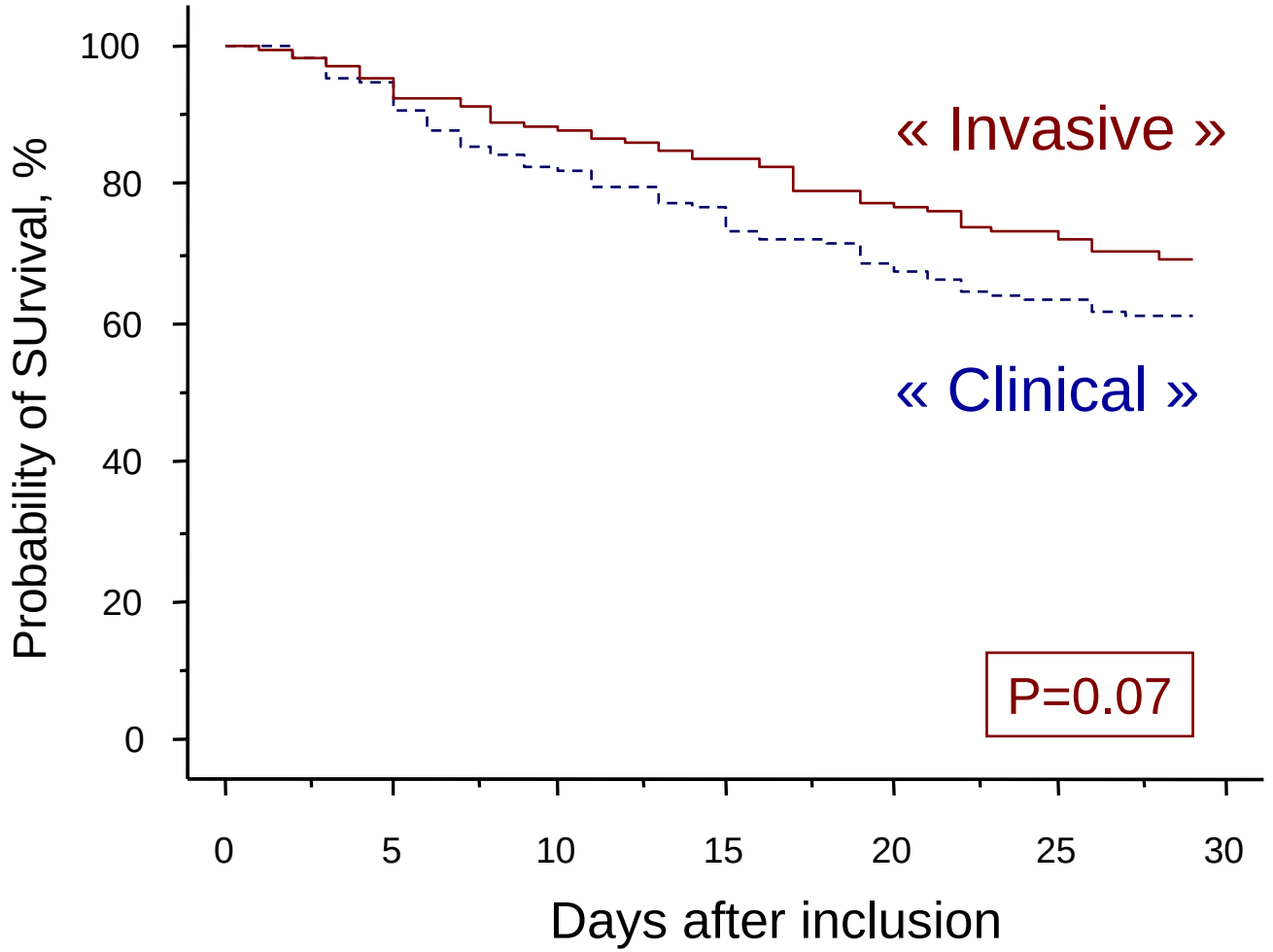
Non-invasive vs. 'invasive' microbiological investigation in VAP

	"Invasive"(n=204)	"Clinical" (n=209)	p value
SAPS II	44 ± 15	42 ± 14	ns
Length prior MV	10.4 ± 10.2	10.7 ± 10	ns
Prior AB Rx	105 (51)	103 (49)	ns
Shock	74 (36%)	81 (38%)	ns
Positive culture	44%	86%	ns
Mortality 14/28d	33%/63%	54%/81%	0.02/0.1
Antibiotic-free days	11.5 ± 9	7.5 ± 7.6	<0.001
Candida colonization	11%	22%	0.0025

Fagon et al, Ann Intern Med 2000; 132: 621-30

Survival According to Diagnostic Strategy of VAP

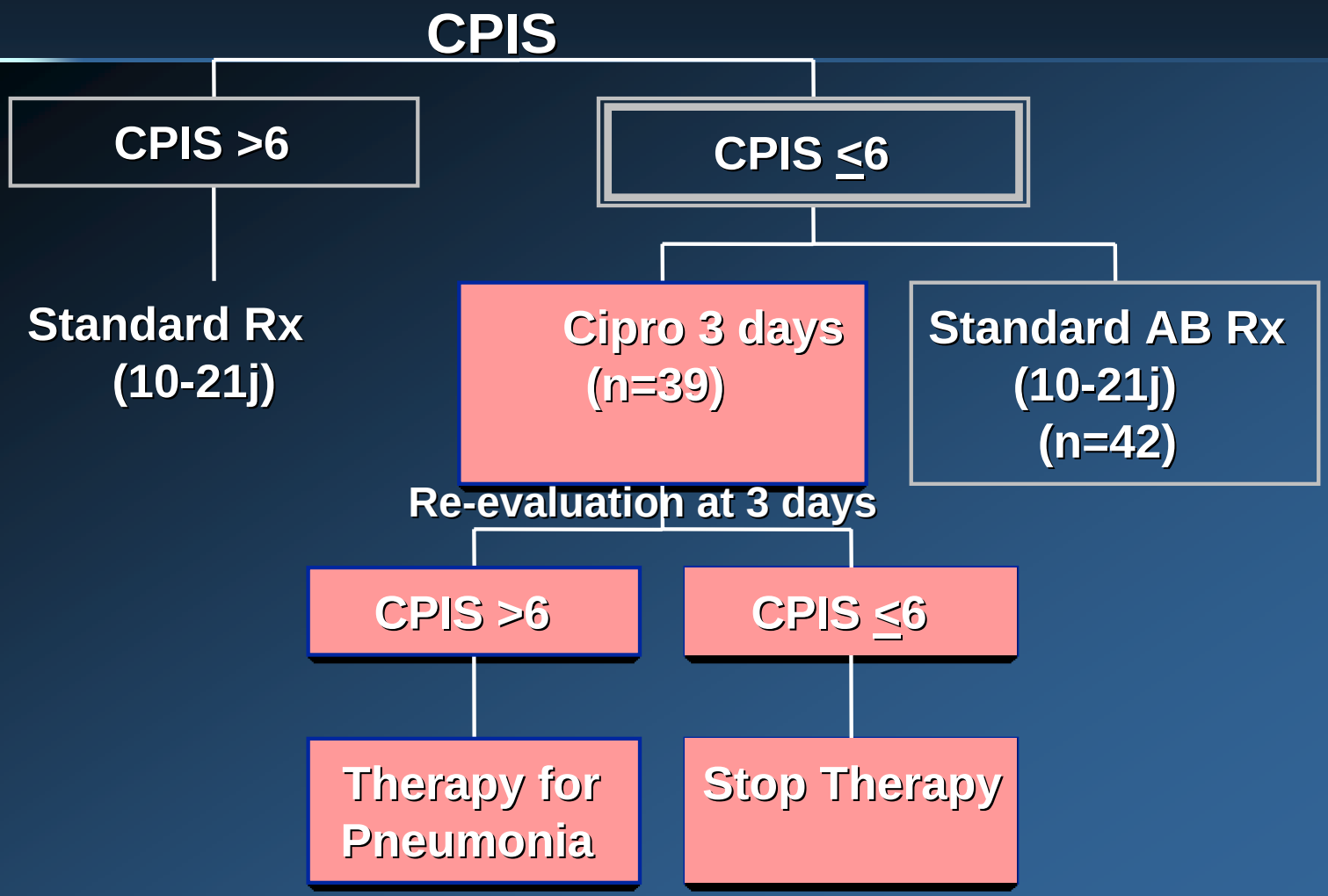
Fagon, Chastre, Wolff, et al. *Ann Intern Med 2000*



Antibiothérapie probabiliste

DESESCALADE

Indications for Empirical Therapy and Importance of Re-evaluation



Singh et al, *AJRCCM 2000; 162: 505-11*

Empirical Therapy and Re-evaluation: Antibiotic use, costs, and resistance

	Experimental (n=39)	Standard (n=42)	p value
CPIS	4.8 ± 1.6	4.9 ± 1.8	ns
CPIS >6 à 3j	8 (21%)	9 (23%)	ns
Extrapulm. Inf.	7 (18%)	6 (15%)	ns
Antibiotics >3d	11 (28%)	38 (97%)	0.0001
Duration of AB trt c/o pts with CPIS ≤ 6 at D3	3	9.8 (4-20)	0.0001
Total costs	$6,482	$16,004	0.0001
Emergence of resistance or superinfection	5 (14%)	14 (38%)	0.017
Death			
14d	3 (8%)	9 (21%)	
30d	5 (13%)	13 (31%)	0.06

Singh et al, *AJRCCM 2000; 162: 505-11*

Computer-assisted management of antibiotics

	Preintervention	Intervention
No. patients	1136	545
Received antibiotics	766 (67%)	398 (73%)
No. DDD/100 pt-days	185	162
No. Susceptibility mismatches	206	12*
No. drug allergy alerts	146	35*
Excessive dosage, mean no. days	5.9	2.7*
Adverse events	28	4*
CAS followed / overridden	-	203/195

Evans et al., NEJM 1998

Les bonnes questions

- Faut-il "préserver"
  - Certaines classes thérapeutiques ?
  - Certains produits ?
- Non, si risque de "perte de chance" pour le malade
  - Il faut pouvoir le justifier ! Assurer le diagnostic +++
  - Reconsidérer +++ le traitement à 48e heure !!
- Oui dans tous les autres cas
  - Traitement "ciblé"
  - "épargner" : les FQ; la vancomycine; le Tienam...
- Ou adopter le principe de "désescalade" (dossier +++)

Comment obtenir l'optimisation pharmacodynamique ?

En améliorant les index thérapeutiques
C ou AUC / CMI

1. Chercher le "meilleur" antibiotique :
= CMI basses + concentrations "appropriées"

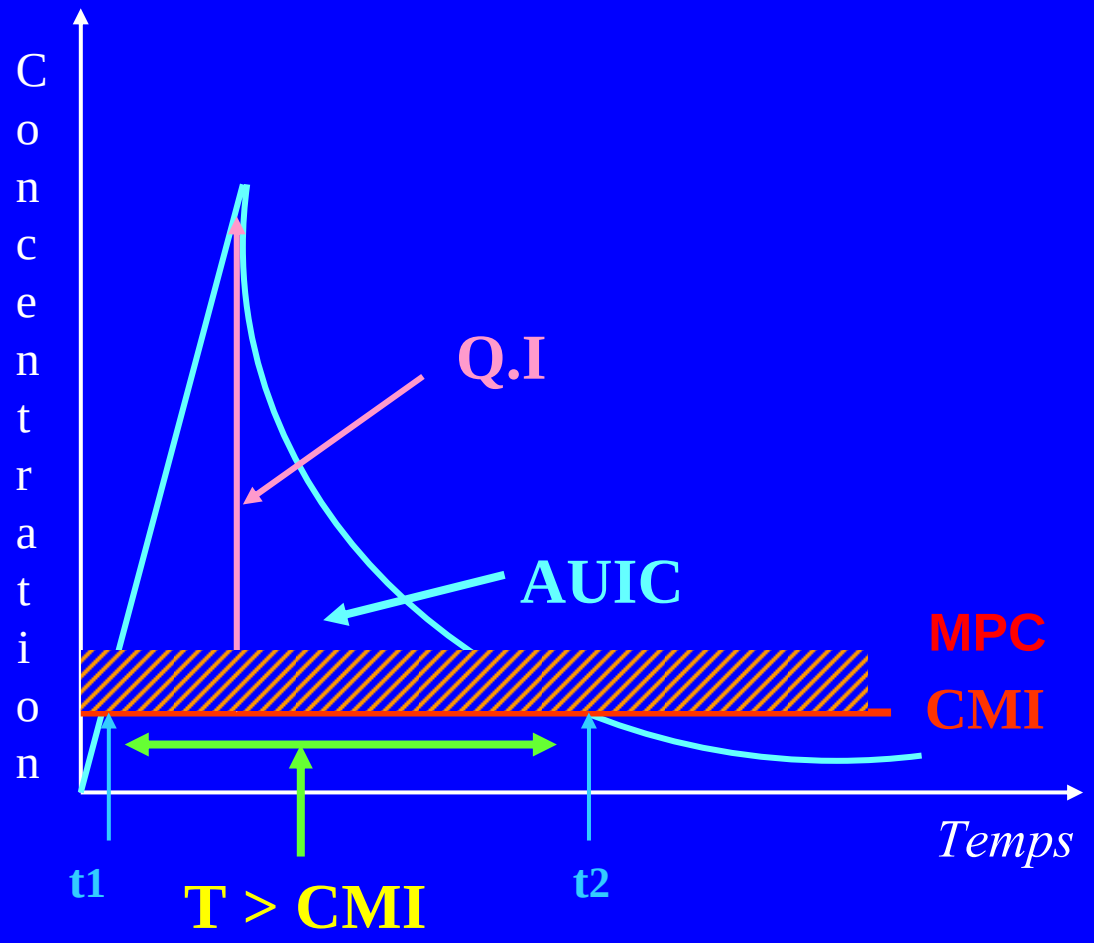
2. Elever les concentrations au site de l'infection : posologies, dose de charge…

3. "Abaisser" les CMI

1. **On ne choisit pas la souche bactérienne responsable de l'infection !!**
2. **Et les associations ??**

Pharmacodynamie et émergence de resistance

MARQUEURS PK/PD



Q.I = Cmax/CMI

AUIC = AUC $_{0 \rightarrow 24\ h}$/CMI

T > CMI = T avec C > CMI

$$AUIC_{0\text{-}24\ h} = \left[1/CMI \int_{t1}^{t2} C(t).dt\right].n$$

Pour la pratique…

- Les concepts de pharmacodynamie et de PK/PD doivent être retenus
- Ils ne sont pas toujours directement applicables, faute d'informations suffisantes
- En revanche, on peut se familiariser
  - Avec les **CMI** des principaux ABT sur les espèces bactériennes les plus fréquemment rencontrées
  - Avec les **concentrations** "attendues" des antibiotiques in vivo
  - Avec les **"marges de manœuvre"** existantes en termes de posologies, d'efficacité et de tolérance

Empirical Antibiotic Choice for the Seriously Ill Patient: Are Minimization of Selection of Resistant Organisms and Maximization of Individual Outcome Mutually Exclusive?

CID 2003; 36 : 1006-12

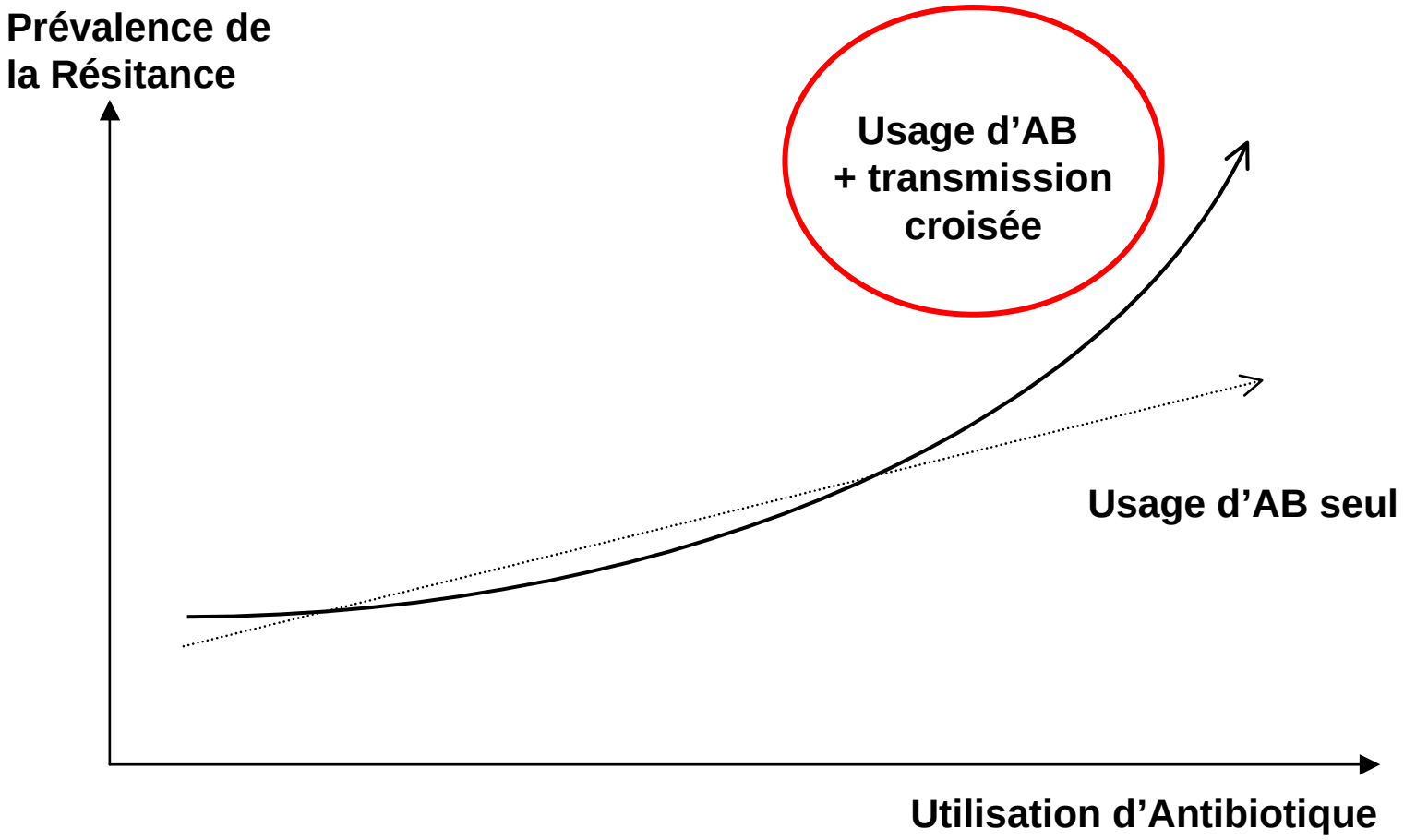
David L. Paterson[1] and Louis B. Rice[2]

- **<u>Strategy 1</u> : Maximizing empirical coverage with subsequent formal reduction in antibiotic therapy**

- **<u>Strategy 2</u> : Alteration in availability of empirical antibiotic choices in response to outbreaks of infection with antibiotic-resistant organisms**

- **<u>Strategy 3</u> : Antibiotic cycling**

Impact de l'Utilisation d'Antibiotiques et de la Transmission Croisée sur la résistance



Antibiotic Prescription for Community-Acquired Pneumonia in the Intensive Care Unit: Impact of Adherence to Infectious Diseases Society of America Guidelines on Survival

M. Bodí,[1] A. Rodríguez,[1] J. Solé-Violán,[2] M. C. Gilavert,[1] J. Garnacho,[3] J. Blanquer,[4] J. Jiménez,[3] M. V. de la Torre,[6] J. M. Sirvent,[7] J. Almirall,[8] A. Doblas,[10] J. R. Badía,[9] F. García,[11] A. Mendía,[12] R. Jordá,[13] F. Bobillo,[14] J. Vallés,[16] M. J. Broch,[5] N. Carrasco,[17] M. A. Herranz,[15] and J. Rello,[1] for the Community-Acquired Pneumonia Intensive Care Units (CAPUCI) Study Investigators[a]

CID 2005, 41 : 1709-16

Etude prospective, 15 mois, 33 hôpitaux
529 pts avec PAC sévère, APACHE II = 18.9
Mortalité en réanimation = 27.9 %