Réduction des durées d'antibiothérapie: Quel impact écologique & économique ?

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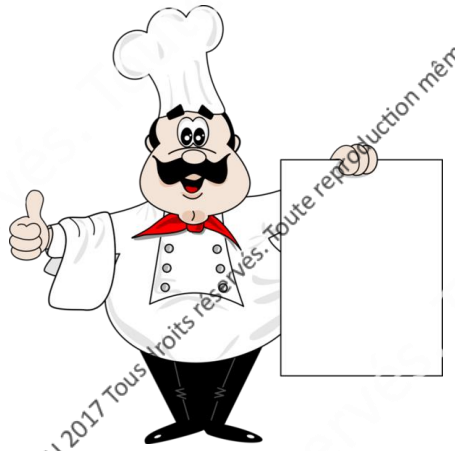
Liens d'intérêt

- **Conseil scientifique / financement recherche ou congrès**
  - Gilead
  - MSD
  - Astellas
  - AstraZeneca
  - Coreviome
  - Pfizer
  - The Medicines Company

Menu

- **Que peut-on espérer en termes de réduction de consommation d'ATB en France ?**
- **Impact économique**
- **Impact écologique**
  - Moins de résistance ?
  - Moins de *C. difficile* ?
  - Impact sur l'environnement



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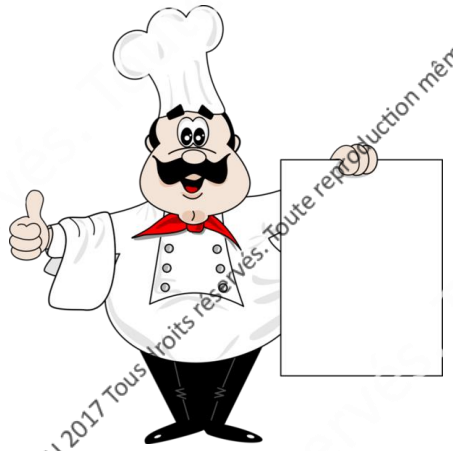

The Maxwell Finland Lecture: For the Duration—Rational Antibiotic Administration in an Era of Antimicrobial Resistance and *Clostridium difficile*

Louis B. Rice

Medical Service, Louis Stokes Cleveland Veterans Affairs Medical Center, and Case Western Reserve University, Cleveland, Ohio

'Among available strategies to reduce use, reductions in length of antimicrobial regimens are the safest and are likely to be the most palatable to practicing clinicians.'

Rice LB. Clin Infect Dis 2008

Le concept des ‘Low hanging fruits’

Usage inapproprié des ATB à l'hôpital

- Etude prospective
- Observationnelle
- Cleveland, USA
- **Audit**
  - 1941 jours d'ATB
  - **576 (30%) 'pas nécessaire'**

Table 2. Reasons for Unnecessary Days of Therapy for All Antimicrobials and the Subset of Agents With Antianaerobic Activity

Reason	No. (%) of Patients	
	All Antimicrobials	Antianaerobic Antibiotics
Noninfectious or nonbacterial syndrome	187 (32)	74 (36)
Treatment of colonization or contamination	94 (16)	25 (12)
Duration of therapy longer than necessary	192 (33)	67 (33)
For treatment regimens*	153	56
For empiric regimens†	39	11
Adjustment not made in a timely manner	20 (3)	9 (4)
Redundant antimicrobial coverage	60 (10)	18 (9)
Spectrum of activity not indicated‡	23 (4)	10 (5)
Total	**576**	**203**

Hecker MT et al. Arch Intern Med 2003

Impact of an Antimicrobial Stewardship Intervention on Shortening the Duration of Therapy for Community-Acquired Pneumonia

Edina Avdic,[1] Lisa A. Cushinotto,[4] Andrew H. Hughes,[2] Amanda R. Hansen,[5] Leigh E. Efird,[1] John G. Bartlett,[2,3] and Sara E. Cosgrove[2,3]

Table 3. Outcomes in Patients With Final Diagnosis of Community-Acquired Pneumonia

Variable	Preintervention (2008) (n = 56)[a]	Intervention (2010) (n = 63)[a]	*P*
Length of stay, median, days	4 days	5 days	
Duration of antibiotic therapy, median (IQR), days	10 (8–13)	7 (7–8)	<.001
Duration of antibiotic therapy, No.			
≤5 days	1	8	<.001
6–7 days	7	28	
8–10 days	24	18	
11–14 days	15	9	
>14 days	9	0	
Excess antibiotic days, total, days	241	93	

Avdic E et al. Clin Infect Dis 2012

Un exemple de CHU Français

- **Enquête ATB ‘un jour donné’, CHU Rennes, 2013**

  - **Durées modales ATB déclarées**
    - 14 jours pour pyelonéphrites
    - 7-10 jours pour pneumopathies ou décompensations BPCO
    - 7-10 jours pour infections intra-abdominales

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Table 1. Estimated Annual Cost Savings in the United States with a Fixed, 4-Day Treatment for Abdominal Sepsis.

Antibiotic	Patients Who Received the Antibiotic	Antibiotic-Days Saved*	Cost Savings†
	percent	*days*	*2015 U.S. $*
Piperacillin–tazobactam	55	660,000	55,367,400
Metronidazole	31	372,000	1,257,360
Ciprofloxacin	27	324,000	1,046,520
Vancomycin	25	300,000	7,200,000
Fluconazole	15	180,000	1,440,000
Ertapenem	10	120,000	30,720,000

* This value is the percentage of patients who received the antibiotic multiplied by 300,000 patients and then multiplied by 4 days.

† Cost savings were calculated as daily charges at Walgreens on April 29,

Paul Ehrlich, 1885

Wenzel RP et al. N Engl J Med 2015

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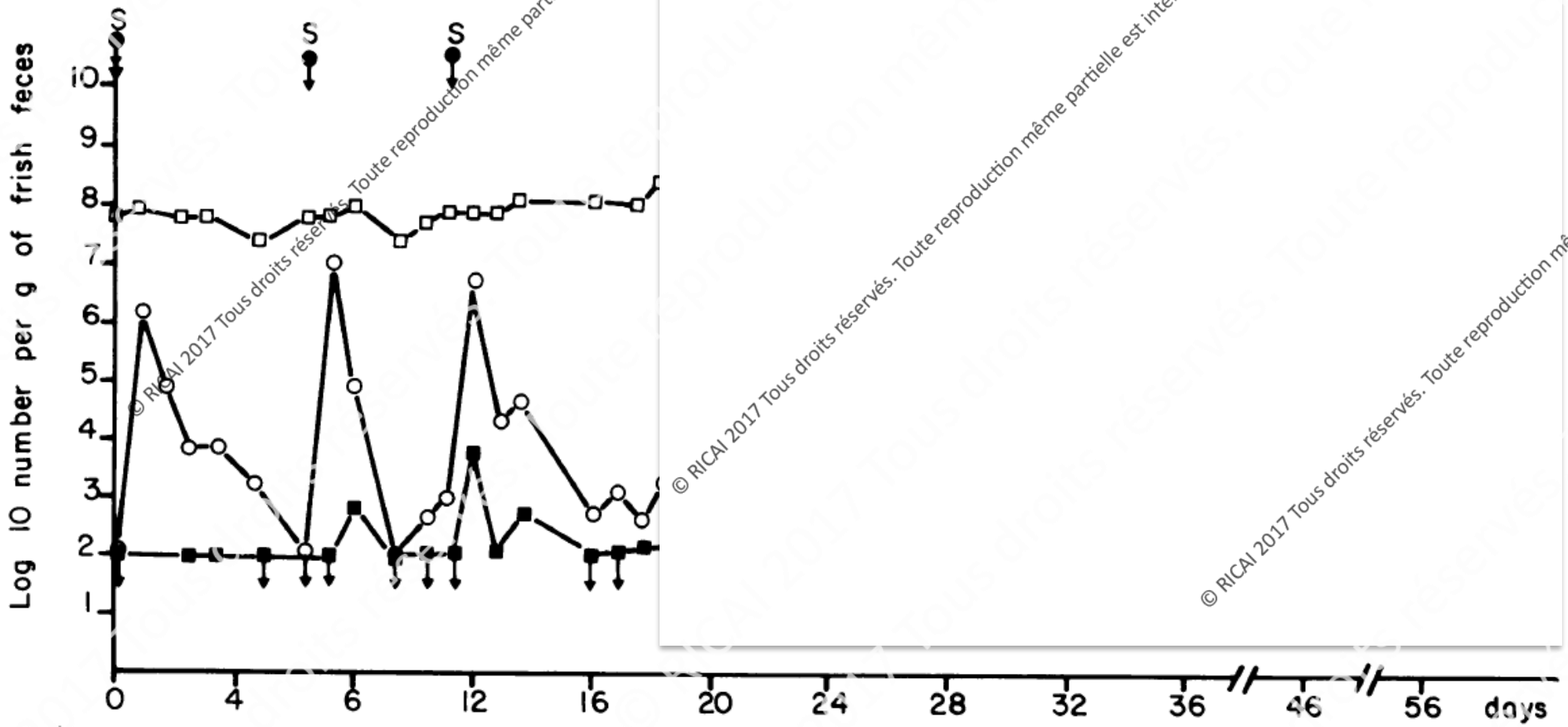
Impact écologique

Est-ce que la durée d'ATB a un impact sur le risque d'émergence de résistances ?

Pas sûr…

Inoculation of penicillinase-producing *Serratia liquefaciens*

- Penicillinase-producing *S. liquefaciens*
- Multi-susceptible *E. coli*



Duval-Iflah Y, Infect Immun 1980

Inoculation of penicillinase-producing *Serratia liquefaciens*

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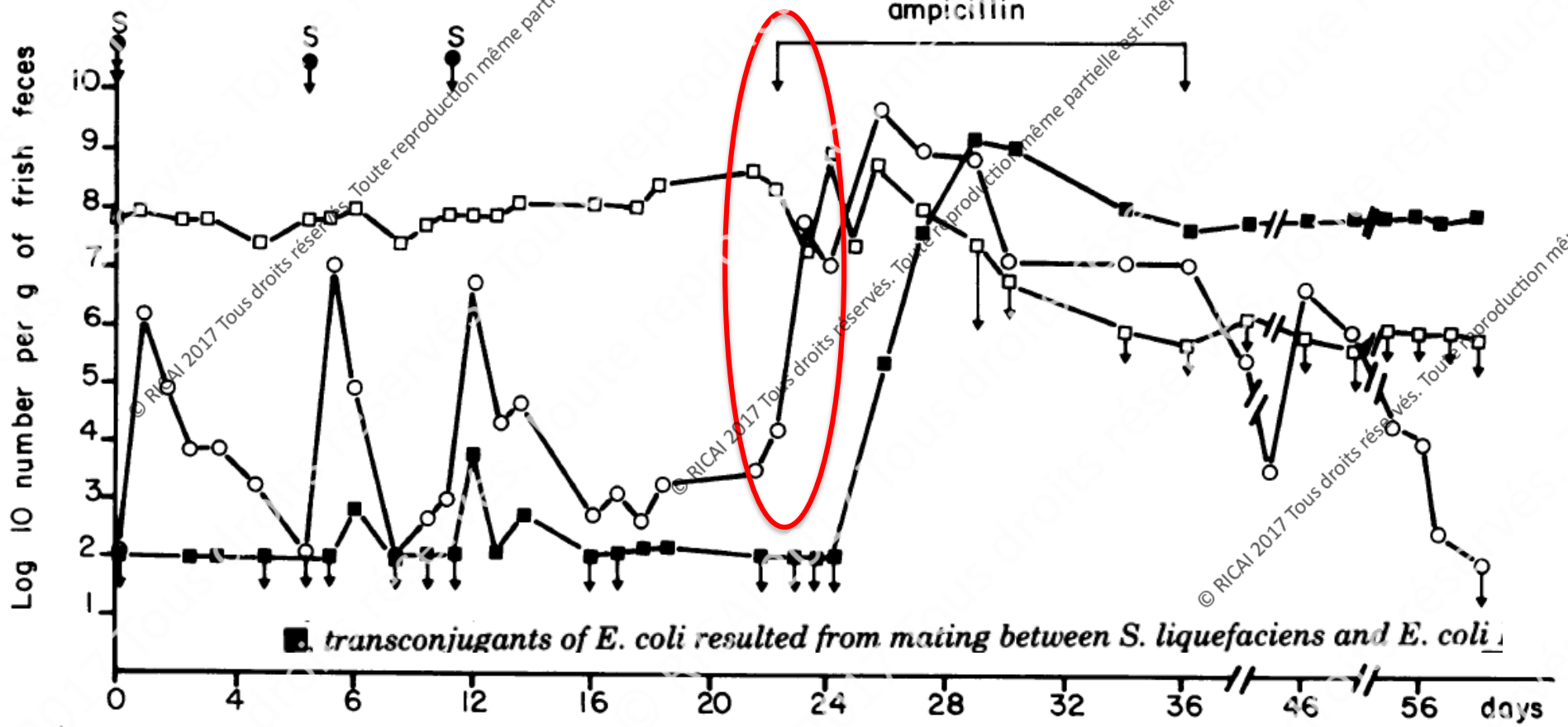
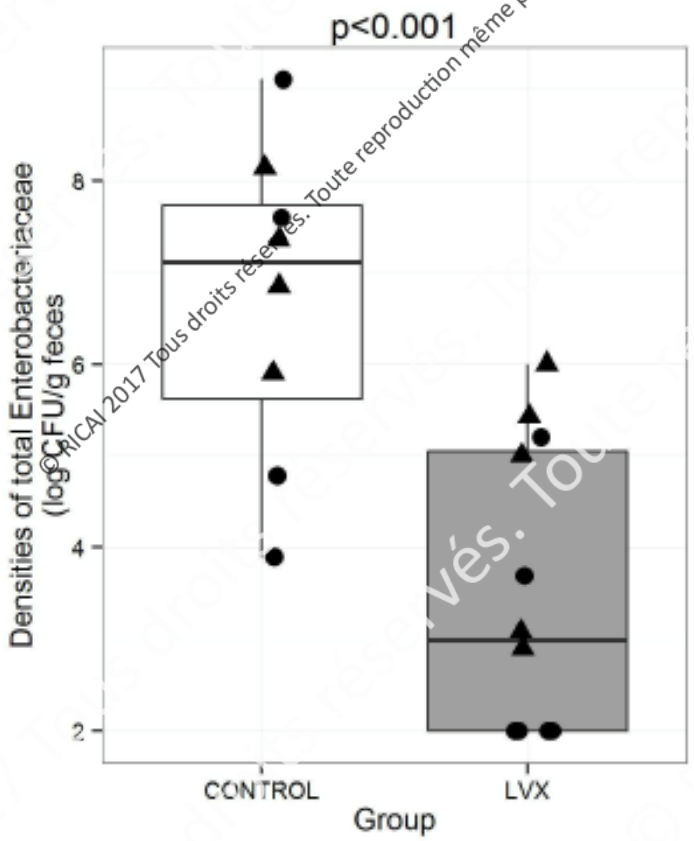


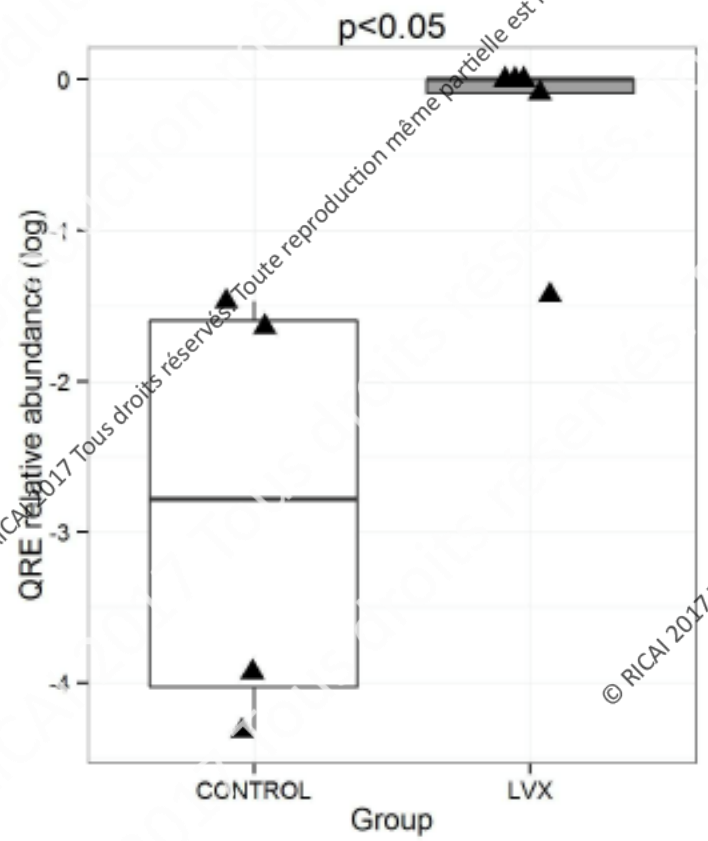
Duval-Iflah Y, Infect Immun 1980

Impact of a short exposure to levofloxacin on faecal densities and relative abundance of total and quinolone-resistant *Enterobacteriaceae*

Julien Bernard, Laurence Armand-Lefèvre, Elsa Luce, Assiya El Mniai, Françoise Chau, Enrique Casalino, Antoine Andremont, Etienne Ruppé

Emergence précoce (< J3 lévofloxacine) d'entérobactéries FQ-R





Bernard J et al. Clin Microbiol Infect 2016

Emergence d'*E. coli* FQ-R sous cipro (PO, 14 j)

GROUP 1 GROUP 3

(V1-33) (V43) (V34-40; V42) (V44, V45) (V41) (V46) (V47,48)

'*Our results suggest that* ***exogenous acquisition of resistant strains when ciprofloxacin concentrations fall within the selective window*** *plays an important role*'

La résistance apparaît à l'atterrissage

De Lastours V, J Infect Dis 2012

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans,

Durée médiane ATB

- 4 j (IQR 4-5)
- 8 j (IQR 5-10)

Variable	Control Group (N=260)	Experimental Group (N=257)	P Value
Primary outcome: surgical-site infection, recurrent intraabdominal infection, or death — no. (%)	58 (22.3)	56 (21.8)	0.92
Secondary outcome			
Surgical-site infection or recurrent intraabdominal infection with resistant pathogen — no. (%)	9 (3.5)	6 (2.3)	0.62
Clostridium difficile infection — no. (%)	3 (1.2)	5 (1.9)	0.71
Extraabdominal infection with resistant pathogen — no. (%)	6 (2.3)	2 (0.8)	0.29

Sawyer RG et al. N Engl J Med 2015

Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial

Louis Bernard, Aurélien Dinh, Idir Ghout, David Simo, Valerie Zeller, Bertrand Issartel, Vincent Le Moing, Nadia Belmatoug, Philippe Lesprit,

	6-week regimen (n=176)	12-week regimen (n=175)	Total (n=351)	p value
Adverse events	51 (29%)	50 (29%)	101 (29%)	1
Death	14 (8%)	12 (7%)	26 (7%)	0·85
Cardiorespiratory failure	7 (4%)	12 (7%)	19 (5%)	0·33
Digestive tract bleeding	4 (2%)	2 (1%)	6 (2%)	0·68
Clostridium difficile infection	2 (1%)	2 (1%)	4 (2%)	1
Antibiotic intolerance	12 (7%)	9 (5%)	21 (6%)	0·66

Bernard L et al. Lancet 2014

Impact of de-escalation of beta-lactam antibiotics on the emergence of antibiotic resistance in ICU patients: a retrospective observational study

Liesbet De Bus[1*], Wouter Denys[1], Julie Catteeuw[1], Bram Gadeyne[1], Karel Vermeulen[2], Jerina Boelens[3], Geert Claeys[3], Jan J. De Waele[1], Johan Decruyenaere[1] and Pieter O. Depuydt[1,4]

Etude prospective observationnelle, réanimation

Patient outcome	Treatment				*p* value
	Total ($n = 344$)	Continuation ($n = 221$, 64%)	De-escalation ($n = 85$, 25%)	Escalation ($n = 38$; 11%)	De-escalation vs. continuation
Antibiotic treatment duration in the ICU for the infection under study (days)	6 (5–9)	5 (4–7)	8 (6–10)	11 (8–19)	<0.001
Total antibiotic consumption in the ICU (days)	10 (5–20)	7 (4–15)	12 (7–32)	24 (15–39)	<0.001
Antibiotic-free days (14 days after onset of infection)[a] ($n = 116$)	1 (0–4)	2 (0–6)	1 (0–3)	0 (0–1)	0.04
Emergence of pathogens resistant to the initial BL therapy	112 (32.6 %)	68 (30.8 %)	29 (34.1 %)	15 (39.5 %)	0.57

De Bus L et al. Crit Care Med 2016

Emergence of Imipenem-Resistant Gram-Negative Bacilli in Intestinal Flora of Intensive Care Patients

Laurence Armand-Lefèvre,[a,b] Cécile Angebault,[a,b] François Barbier,[b,c] Emilie Hamelet,[a] Gilles Defrance,[a] Etienne Ruppé,[a,b] Régis Bronchard,[d] Raphaël Lepeule,[b] Jean-Christophe Lucet,[e] Assiya El Mniai,[a] Michel Wolff,[c] Philippe Montravers,[d] Patrick Plésiat,[f] Antoine Andremont[a,b]

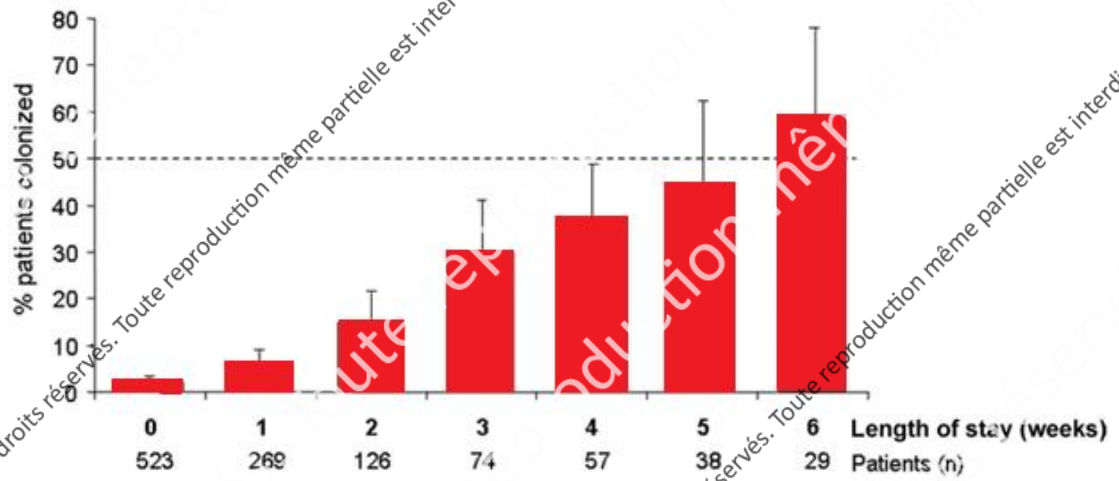


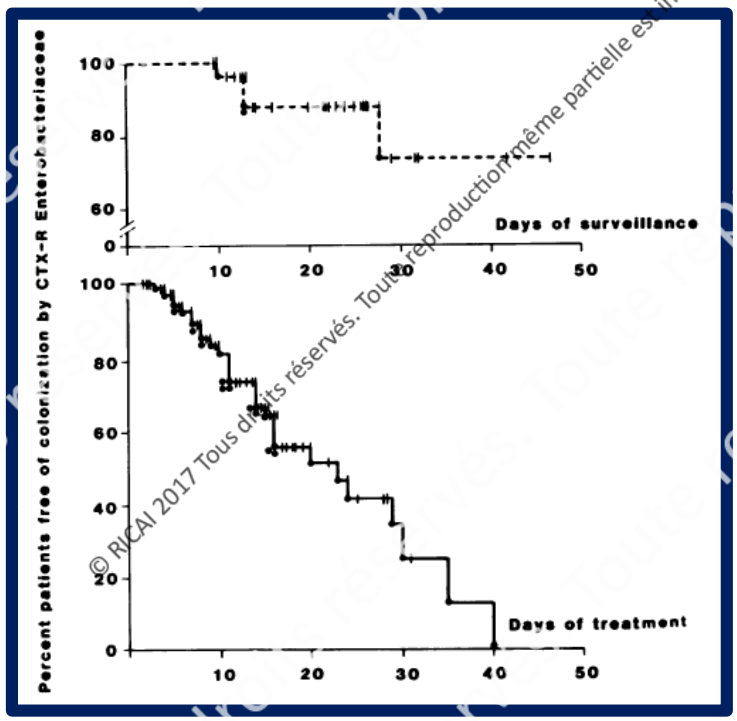
FIG 1 Rates of intestinal colonization by imipenem-resistant gram-negative bacilli in intensive care patients. Bars indicate observed rates ± standard deviation (SD) (error bars).

Characteristic or outcome	No. of individuals or parameter value (%, unless range is specified)				
	Carrier patients (n = 22 (%))	Controls (n = 22)	Univariate OR[a]	Univariate P[b]	Multivariate OR[c]
Days of imipenem exposure				0.09	
0	5 (22.7)	12 (54.5)	1.0		1.0
1 to 3	8 (36.4)	6 (27.3)	3.1 (0.6–18.3)		5.3 (1.0–38.4)
4 to 21	9 (40.9)	4 (18.2)	5.1 (0.9–35.1)		6.8 (1.2–50.2)

Armand-Lefebvre L et al. Antimicrob Agents Chemother 2011

La durée d'ATB est un FDR de résistance

Durée de l'antibiothérapie et résistance



Prevot et al, AAC 1986

Table 3. Multivariate analysis of risk factors associated with infection or colonization with multidrug-resistant *Pseudomonas aeruginosa* (MDRPA) among patients hospitalized in intensive care units.

Variable	OR (95% CI)	
	Initial model	Final model
Receipt of hemodiafiltration or hemodialysis	3.05 (1.03–10.4)	…
Receipt of piperacillin or ticarcillin	4.13 (0.78–21.8)	…
Receipt of imipenem for duration longer than the median[a]	4.05 (1.26–13.1)	3.17 (0.92–10.9)
Receipt of ciprofloxacin for duration longer than the median[a]	53.7 (2.94–114)	11.0 (1.27–32.9)
Receipt of metronidazole	3.56 (1.01–12.7)	…

Paramythioutou et al, Clin infect dis 2003

Cumulative Antibiotic Exposures Over Time and the Risk of *Clostridium difficile* Infection

Vanessa Stevens,[1,3,4] Ghinwa Dumyati,[2] Lynn S. Fine,[2] Susan G. Fisher,[3] and Edwin van Wijngaarden[3]

	CDI positive *n* (%)	CDI negative *n* (%)	Adjusted hazard ratio (95% CI)
Defined daily doses[e], median (IQR)	14.8 (21.2)	7.2 (12.3)	—
<3.0	18 (7)	1502 (16)	Ref
3.0 to 7.79	49 (20)	3702 (37)	1.2 (.7, 2.1)
7.80 to 21.0	89 (37)	2952 (30)	2.8 (1.7, 4.6)
>21.0	85 (35)	1757 (18)	5.3 (3.1, 9.0)
Antibiotic days, median (IQR)[f]	14.0 (23.0)	7.0 (9.0)	—
<4	22 (9)	2208 (22)	Ref
4 to 7	41 (17)	3071 (31)	1.4 (.8, 2.4)
8 to 18	87 (36)	3097 (31)	3.0 (1.9, 5.0)
>18	91 (38)	1537 (16)	7.8 (4.6, 13.4)
Number of antibiotics, median (IQR)[f]	3.0 (4.0)	2.0 (2.0)	—
1	31 (13)	3744 (38)	Ref
2	54 (22)	2507 (25)	2.5 (1.6, 4.0)
3 or 4	70 (29)	2505 (25)	3.3 (2.2, 5.2)
5 or more	86 (36)	1157 (12)	9.6 (6.1, 15.1)

Stevens D et al. Clin Infect Dis 2011

Corrélations durées de traitement / émergence résistance

Table 6.—Odds Ratios for Penicillin-Resistant *Streptococcus pneumoniae* (PRSp) Carriage According to Daily Dose and Duration of the Last Antibiotic Used During the Previous 30 Days*

Variable	No. of Children	No. of PRSp Carriers	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Last β-lactam						
Daily dose						
No use†	780	10	1.0		1.0	
Low†	84	6	5.9 (2.1-16.7)	.002	7.5 (2.5-22.8)	<.001
High	54	0	NA	.9	NI	
Missing‡	23	0	NA	.9	NI	
Duration of treatment						
No use†	780	10	1.0		1.0	
Long†	138	6	3.5 (1.3-9.8)	.02	3.9 (1.4-11.2)	.01
Short	23	0	NA	.9	NI	

Si traitement bêta-lactamine > 5 j dans les 30 j précédents,
=> OR portage PSDP = 3.9 [1.4-11.2]

Guillemot D et al. JAMA 1998

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Review

What happens in hospitals does not stay in hospitals: antibiotic-resistant bacteria in hospital wastewater systems

D. Hocquet [a,b,*], A. Muller [a,b], X. Bertrand [a,b]

Durées ATB ajustées => - 30% consommation ATB (ville & hôpitaux)
=> - 30% ATB relargués dans les environnements

Hocquet D et al. J Hosp Infect 2016

Durées de Traitement: Conclusions

- **Diminuer la durée de traitement des infections courantes est un des moyens les + simples pour réduire les consommations**
  - **Bien mieux accepté que la non-prescription**
  - **Efficacité équivalente bien démontrée (PAC, pyélo, érysipèle, etc.)**
- **L'impact sur le risque de résistance/*C. difficile* n'est pas évident**
- **Néanmoins bénéfique (autres EI, coût, environnement, moral)**
- **Réduire les durées n'est qu'une pièce de l'édifice 'bon usage' !**

Questions ?