Inhaled antimicrobial therapy: pharmacodynamics and risks for development of resistance

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"Pulmonary infections"

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- Speaking fees
  - Bayer, GSK
- Decision-making and consultation bodies (current)
  - General Assembly of EUCAST
  - European Medicines Agency (external expert)
  - US National Institutes of Health (grant reviewing)

Slides: http://www.facm.ucl.ac.be → Lectures

Why Inhalation ?

- Novel strategies are required to 'break' the vicious cycle created in local pulmonary infections where exacerbations and recurrences are common and cause disease progression[1]

1. Smith MP. *J R Coll Physicians Edinb* 2011;41:132

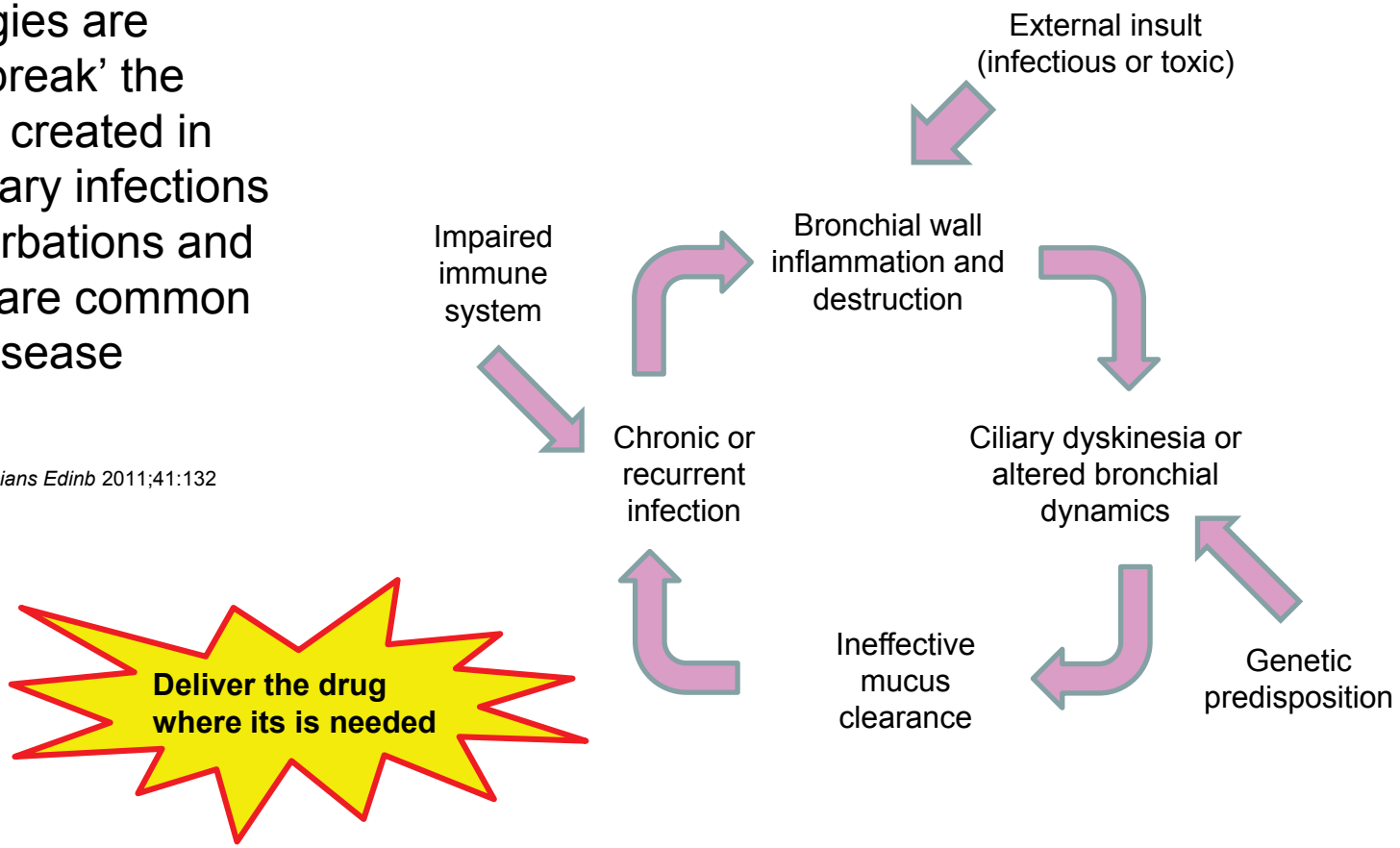


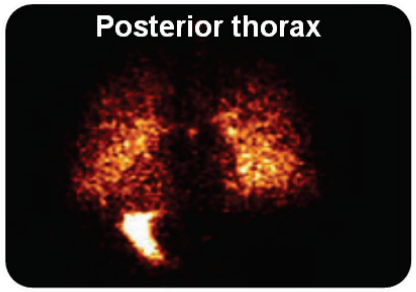
Figure adapted by kind permission of Dr Diane Bilton, Royal Brompton Hospital, London

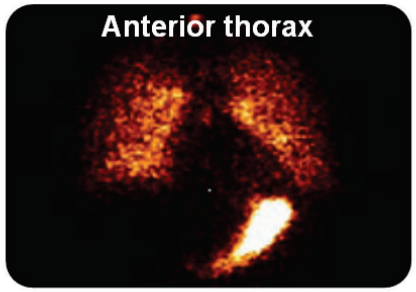
Trying to reach deep in lung …

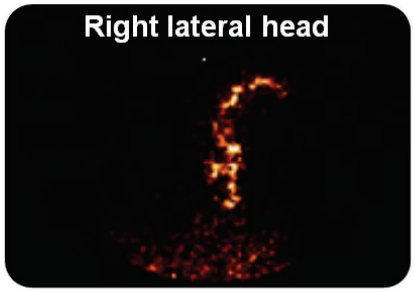
An example with amikacin

	Deposition of nominal dose, [%]: mean (SD) Amikacin Inhale 400 mg (n=13*)
Lung	43.1 (6.1)
Oropharyngeal	29.4 (7.4)
Remaining in device	16.1 (4.8)
Exhaled air	11.5 (5.5)

Scintigraphy scans after administration of a single dose of 400 mg ^{99m}Technetium labelled Amikacin Inhale in one representative subject

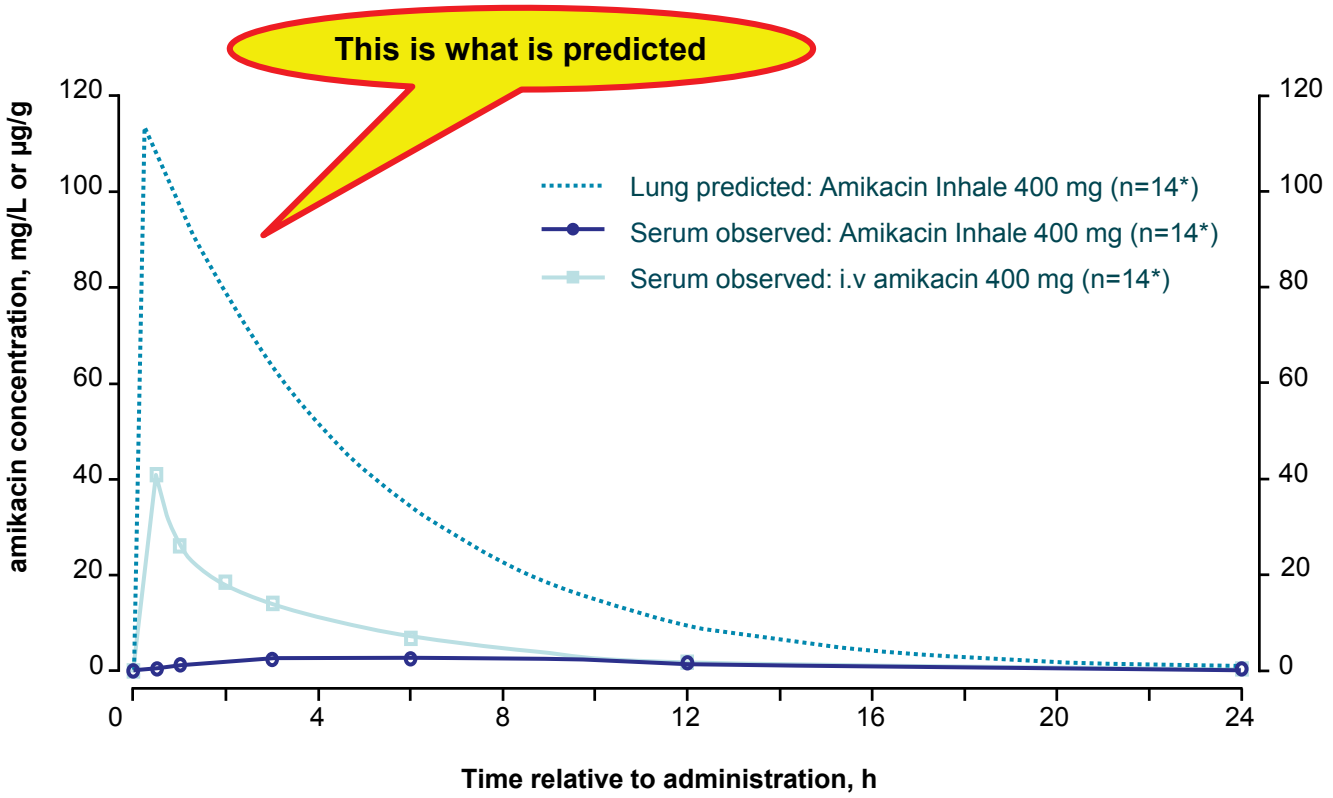






Corkery K et al. ATS 2008 Poster 517

Can you achieve high local concentrations ?



Amikacin lung (predicted by scintigraphy) and mean serum-time profiles after single doses of Amikacin Inhale (Amikacin Inhalation Solution 400 mg administered via the PDDS hand-held device) and IV amikacin 400 mg infusion in healthy volunteers.
*Evaluable subjects

1. Corkery K et al. ATS 2008. Poster 517; 2. Eldon M et al. ISICEM 2008. Poster A135

Where do we go to now ?

CMR
Journals.ASM.org
October 2014 Volume 27 Number 4 Clinical Microbiology Reviews p. 753–782

Pharmacokinetics and Pharmacodynamics of Aerosolized Antibacterial Agents in Chronically Infected Cystic Fibrosis Patients

Axel Dalhoff
University Medical Center Schleswig-Holstein, Institute for Infection Medicine, Kiel, Germany

Where do we go to now ?

CMR
Journals.ASM.org
October 20

Pharmacokinetic
Agents in Chron

Axel Dalhoff
University Medical Center Schleswig-H

MICs can be very high…

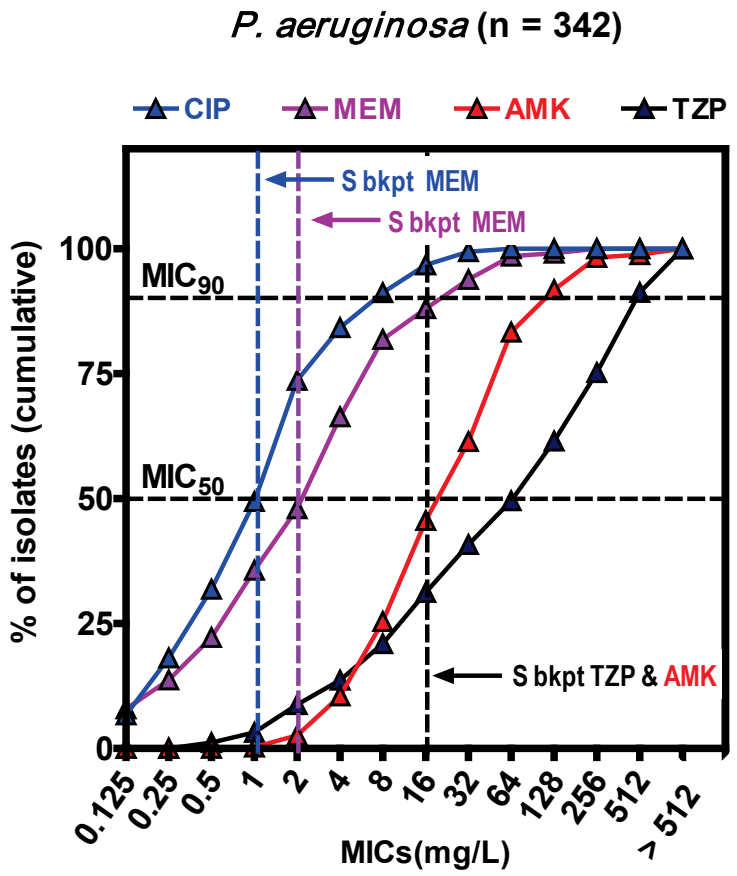
TABLE 1 Antibacterial activities of various agents inhibiting 50% and 90% of strains isolated from CF patients[a]

	Concn (mg/liter)											
	CPX		LVX		Tobramycin		Amikacin		Aztreonam		Colistin	
Organism	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
P. aeruginosa	1–2	8	1–2	8	0.5–8	8–256	8–16	>128	4–8	64–128	0.5–2	0.5–8
S. maltophilia	4	16	2	8	>32	>32	128	>128	>128	>128	2	8
B. cepacia	4	32	4	32	>32	>32	128	>128	32	>128	IR	IR
A. xylosoxidans	4	16	4	16	>32	>32	>128	>128	64	>128	8	>16
MRSA	16	>32	4	>32	128	>128	8	16	>512	>512	IR	IR

[a] Data were derived from references 59–70. CPX, ciprofloxacin; LVX, levofloxacin; IR, intrinsically resistant.

Dalhoff, Clin Microb Rev 2014; 27:753-782

MICs can be very high…



Data from an European (FR, UK, BE; DE) collection

Drug	MIC_{50}	MIC_{90}	% S	% R
CIP	1	8	49	51
MEM	2	16	48	52
AMK	32	128	46	54
TZP	64	512	31	69

But here are published concentrations…

TABLE 2 Pharmacokinetics of various antibacterials in adult CF patients following oral, intravenous, or aerosolized administration

Agent, dose, and route	C_{max} (mg/liter) in serum	C_{max} (mg/liter) in sputum	C_{max} (mg/liter) in lung or ELF	$t_{1/2}$ (h) in serum/sputum	Urinary recovery (%)	Reference(s)
CPX, 500 mg, p.o.	2.5–3.8	0.7–1.9	3.9–29	3.7–5.1	35.7	144–146
CPX, 750 mg, p.o.	3.4–4.5		3.6–4.5			144, 145
CPX, 1,000 mg, p.o.	4.6–5.6	1.8		3.7–5.1	40.8	144–147
CPX, 200 mg, i.v.	4.9		16.9			148
CPX, 32.5 mg, ae	0.056	33.0		9.5/9.04		149
LVX, 200 mg, p.o.	2.1		3.9			151
LVX, 500 mg, p.o.	4.1–5.3 (4 h)		9.9–15.2*			152–155
LVX, 750 mg, p.o.	12.0 (4 h)		22.1*			152–155
LVX, 500 mg, i.v.	6.6		18.3			156
LVX, 180 mg, ae	0.95–1.3	2,563-2,932		6.4–6.8/3.5–4.3		157
TOB, 1.7–3.5, mg/kg q.d. i.v.	3.6–11.3 2		1.1-0.7		85	158,160
TOB, 10 mg/kg, q.d. i.v.	22–29			1.7–2.2		221, 223, 224, 369
TOB, 600 mg, ae[b]	1.3			13	17.5	164
TOB, 300 mg, ae[b]	<4	489–695	3.6–5.5	8.9–11.2	5.5	165–168
TOB, 112 mg, ae[c]	1.02	1,048		3.1/2.2		169
TOB, 300 mg, ae[b]	1.04	737		3.0/1.7		169
AMI, 30 mg/kg, i.v.	83–121 (AUC = 235 mg · h/liter)	6.3–10.9 (AUC = 83.7 mg · h/liter)		0.6–2.6	83	369, 225, 299, 370, 371
AMI, 500 mg, ae	AUC = 8.3 mg · h/liter	AUC = 3,830 mg · h/liter		2.9		170
AMI, 560 mg, ae	1.29	2,286			25–50	171
AZM, 2 g	80–228	5.2		1.8	72	172–175
AZM, 75 mg, ae	0.42–0.49	324–677		2.1		176, 177
COL, 2.4 mg/kg	2.5–10 (range)			4.2		179
COL, 66 mg	0.17–0.18	~40		4.1–4.5	4.3	180

[a] The broad range of ciprofloxacin lung tissue concentrations following oral (p.o.) or i.v. administration is due to the fact that some investigators administered the drugs once and others administered them repeatedly; the higher values represent steady-state concentrations. The range of levofloxacin concentrations following aerosolized (ae) administration is due to the fact that the dose of 180 mg was administered in two different formulations (50 mg/ml and 100 mg/ml) (lung, lung tissue homogenate; ELF, epithelial lining fluid; AUC, area under the concentration-versus-time curve; $t_{1/2}$, half-life, either in serum or in sputum; CPX, ciprofloxacin; LVX, levofloxacin; TOB, tobramycin; AMI, amikacin; AZM, aztreonam; COL, colistin). Asterisks indicate values for ELF.

[b] Tobramycin solution for inhalation.

[c] Tobramycin dry powder for inhalation.

Large variations sputum and little in lung/ELF…

TABLE 2 Pharmacok…ation

Agent, dose, and route	C_{max} (mg/liter)	in sputum	in lung or ELF	Reference(s)
CPX, 500 mg, p.o.				144–146
CPX, 750 mg, p.o.				144, 145
CPX, 1,000 mg, p.o.				144–147
CPX, 200 mg, i.v.				148
CPX, 32.5 mg, ae	CPX, 32.5 mg, ae	33.0		149
LVX, 200 mg, p.o.				151
LVX, 500 mg, p.o.	LVX, 180 mg, ae	2,563-2,932		152–155
LVX, 750 mg, p.o.				152–155
LVX, 500 mg, i.v.				156
LVX, 180 mg, ae	TOB, 300 mg, ae[b]	489–695	3.6–5.5	157
TOB, 1.7–3.5, mg/kg q.d	TOB, 112 mg, ae[c]	1,048	3.1/2.2	158,160
TOB, 10 mg/kg, q.d. i.v.	TOB, 300 mg, ae[b]	737	3.0/1.7	221, 223, 224, 369
TOB, 600 mg, ae[b]				164
TOB, 300 mg, ae[b]	AMI, 560 mg, ae	2,286		165–168
TOB, 112 mg, ae[c]				169
TOB, 300 mg, ae[b]	AZM, 75 mg, ae	324–677		169
AMI, 30 mg/kg, i.v.				369, 225, 299, 370, 371
AMI, 500 mg, ae	COL, 66 mg	~40		170
AMI, 560 mg, ae				171
AZM, 2 g				172–175
AZM, 75 mg, ae				176, 177
COL, 2.4 mg/kg				179
COL, 66 mg				180

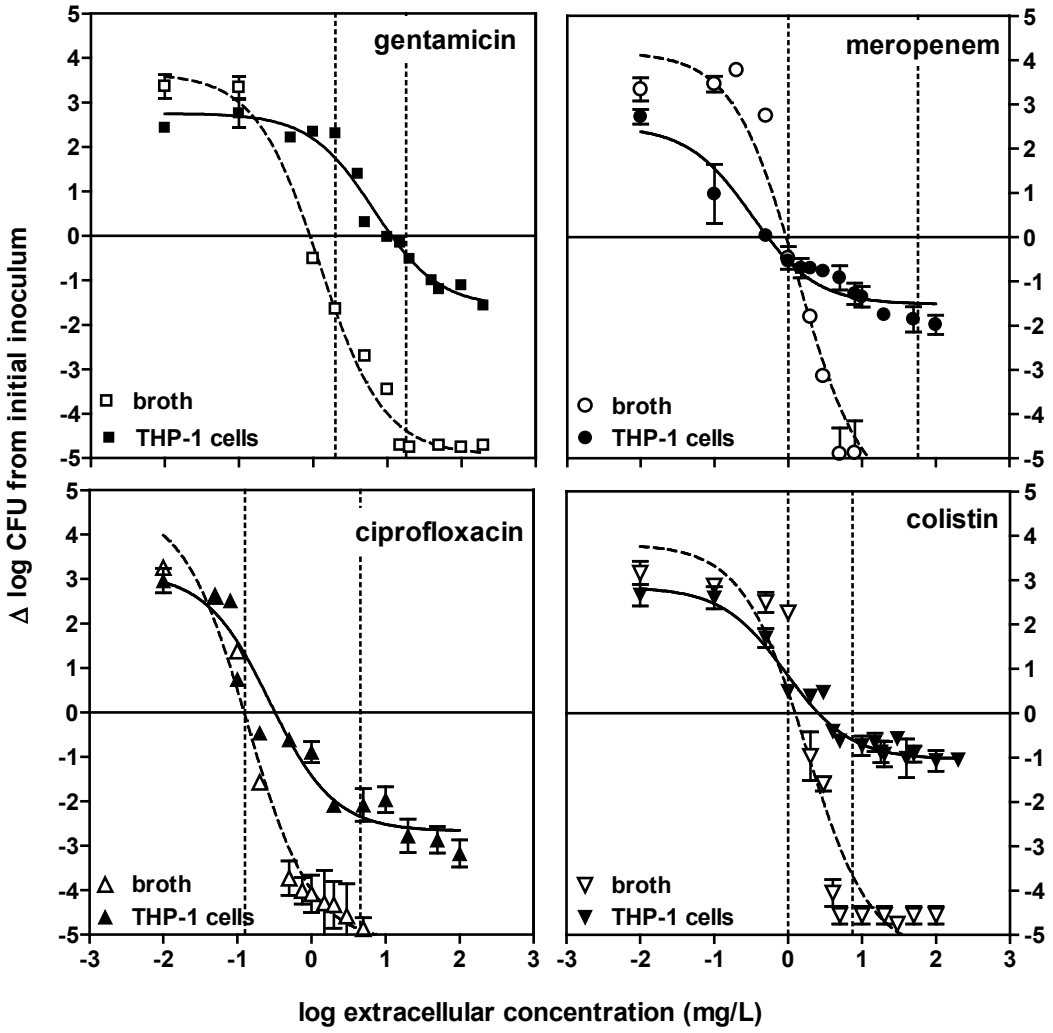
[a] The broad range of cipro…tered the drugs once and others administered them…zed (ae) administration is due to the fact that the do…ithelial lining fluid; AUC, area under the concentration-versus-time curve; $t_{1/2}$, half-life, either in serum or in sputum; CPX, ciprofloxacin; LVX, levofloxacin; TOB, tobramycin; AMI, amikacin; AZM, aztreonam; COL, colistin). Asterisks indicate values for ELF.

[b] Tobramycin solution for inhalation.

[c] Tobramycin dry powder for inhalation.

Would a high concentration help ?

Concentration effects relationships *(P. aeruginosa)*



Concentration--response curves of selected antibiotics against extracellular and intracellular *P. aeruginosa*. The graphs show the change in the number of CFU (Δlog CFU from the initial inoculum) per mL of broth (extracellular, open symbols, dotted lines) or per mg of cell protein (intracellular, closed symbols; plain lines) in THP-1 cells after 24 h incubation at the increasing extracellular concentrations expressed in mg/L (total drug).

The plain horizontal line corresponds to a bacteriostatic effect (no change from initial inoculum).

The vertical dotted lines show the serum MIC-C_{max} range of concentrations..

Buyck *et al.* Antimicrob Agents Chemother. 2013;572310-8.

Would a high concentration help ?

Concentration effects relationships (pharmacology)

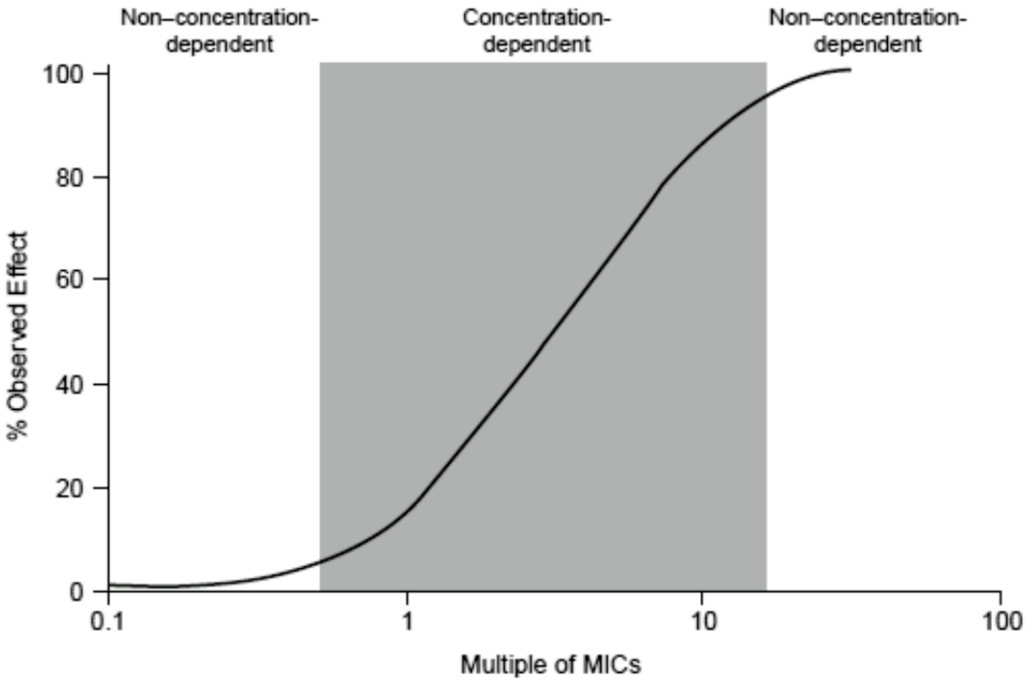


Figure 1. Characteristics of a sigmoidal dose-response curve. MICs = minimum inhibitory concentrations.

Flume & Klepser, **Pharmacotherapy 2002;22(3 Pt 2):71S–79S**.

Would a high concentration help ?

Concentration effects relationships (pharmacology)

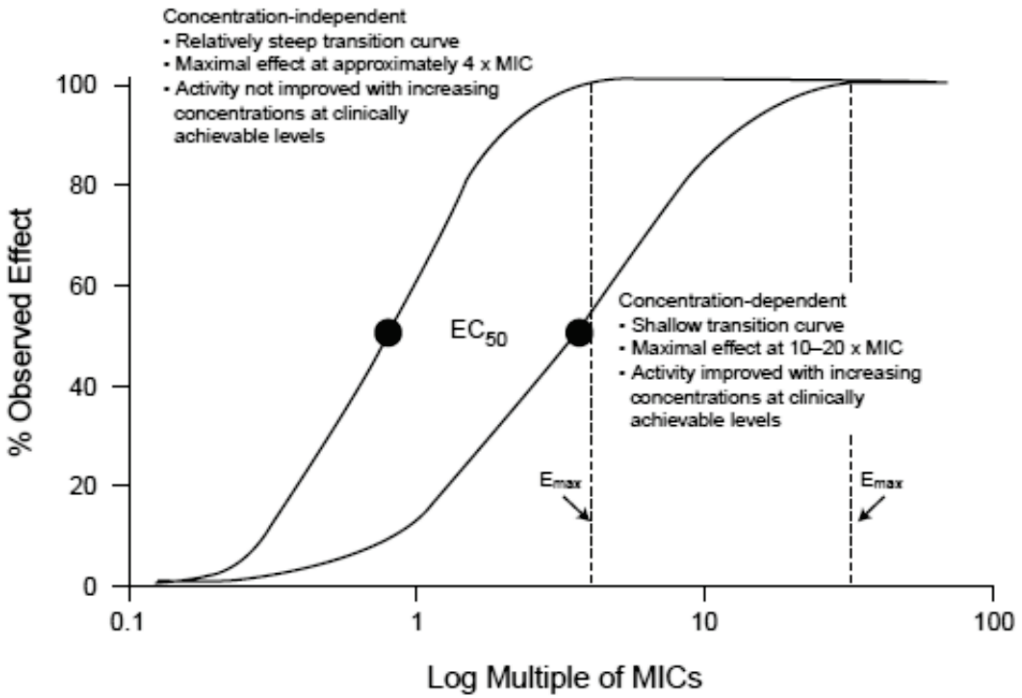
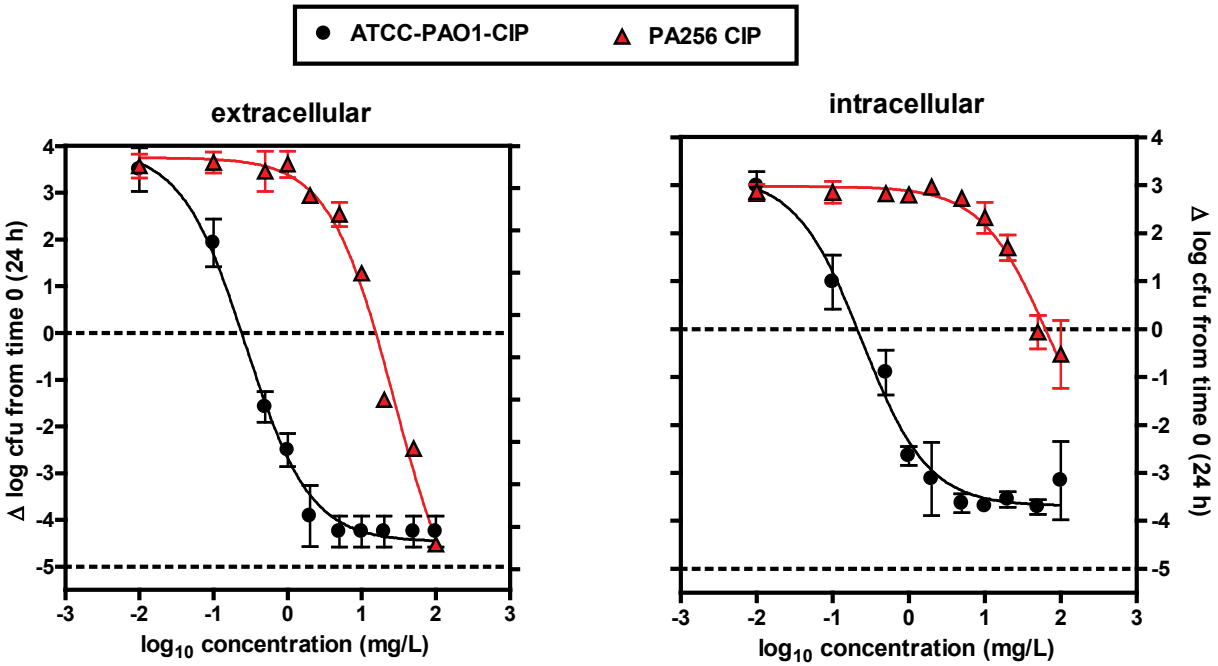


Figure 2. General properties of agents exhibiting concentration-dependent and non–concentration-dependent killing. MICs = minimum inhibitory concentrations; E_{max} = maximal effect; EC_{50} = concentration producing 50% of the maximal effect.

Flume & Klepser, **Pharmacotherapy 2002;22(3 Pt 2):71S–79S**.

High concentration and resistant organisms

Concentration effects relationships (*P. aeruginosa* – ciprofloxacin)

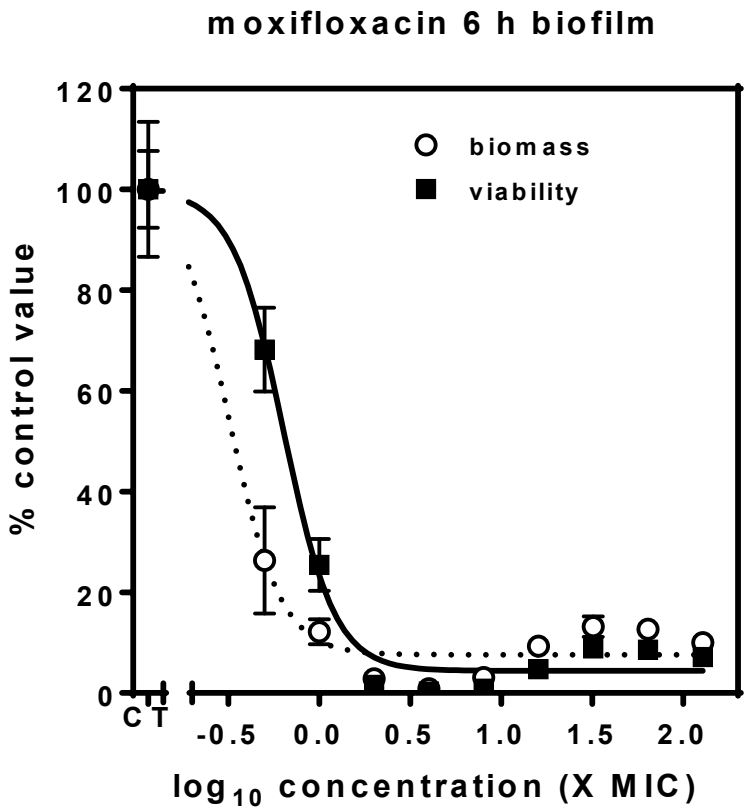


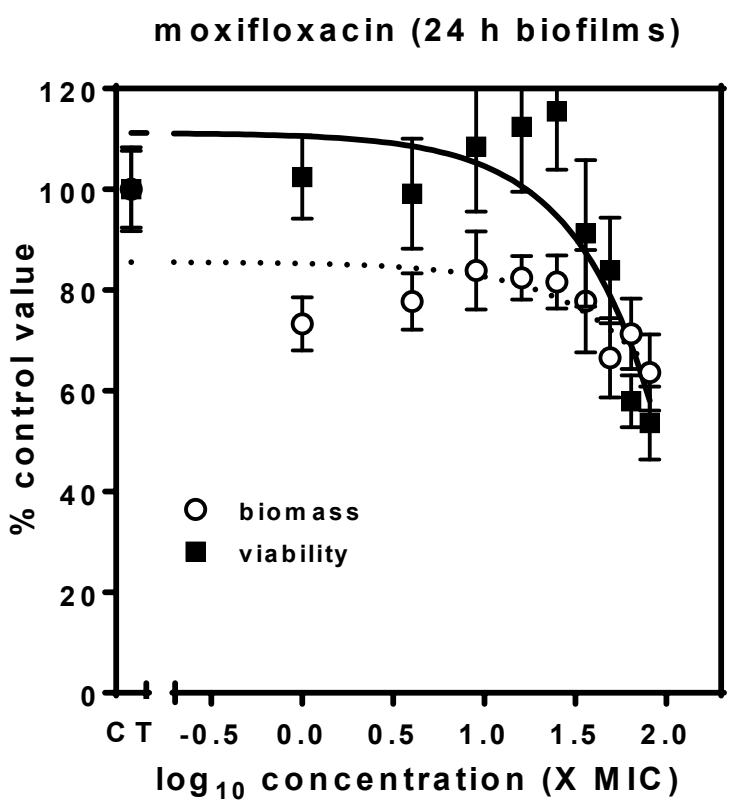
Strain	MIC
PaO1	0.125
PA256	32

Concentration--response curves of selected antibiotics against extracellular and intracellular *P. aeruginosa*. The graphs show the change in the number of CFU (Δlog CFU from the initial inoculum) per mL of broth (extracellular, left) or per mg of cell protein (intracellular, right) in THP-1 cells after 24 h incubation at the increasing extracellular concentrations expressed in mg/L (total drug).
The upper dotted horizontal line corresponds to a bacteriostatic effect (no change from initial inoculum).
The lower dotted horizontal line corresponds to the limit of detection

Buyck *et al. ICAAC 2012 and in preapration*

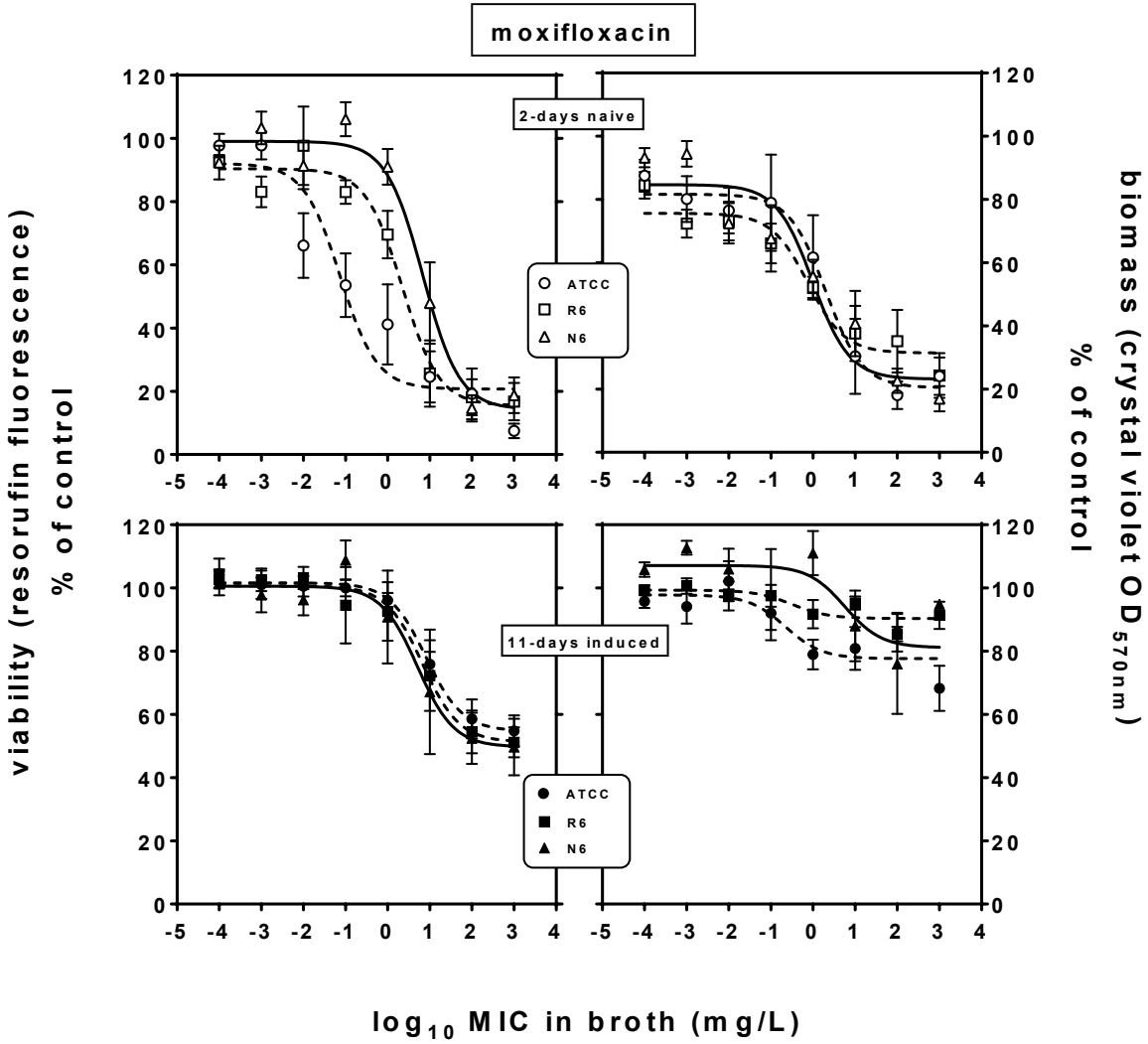
High concentration and biofilm (*S. aureus*)





Adapted from Bauer *et al*. Antimicrob Agents Chemother. 2013;57:2726-37

High concentration and biofilm (*S. pneumoniae*)



Vandevelde *et al*. J Antimicrob Chemother. 2015 Feb 23. pii: dkv032. [Epub ahead of print]

We may need antibiofilm strategies

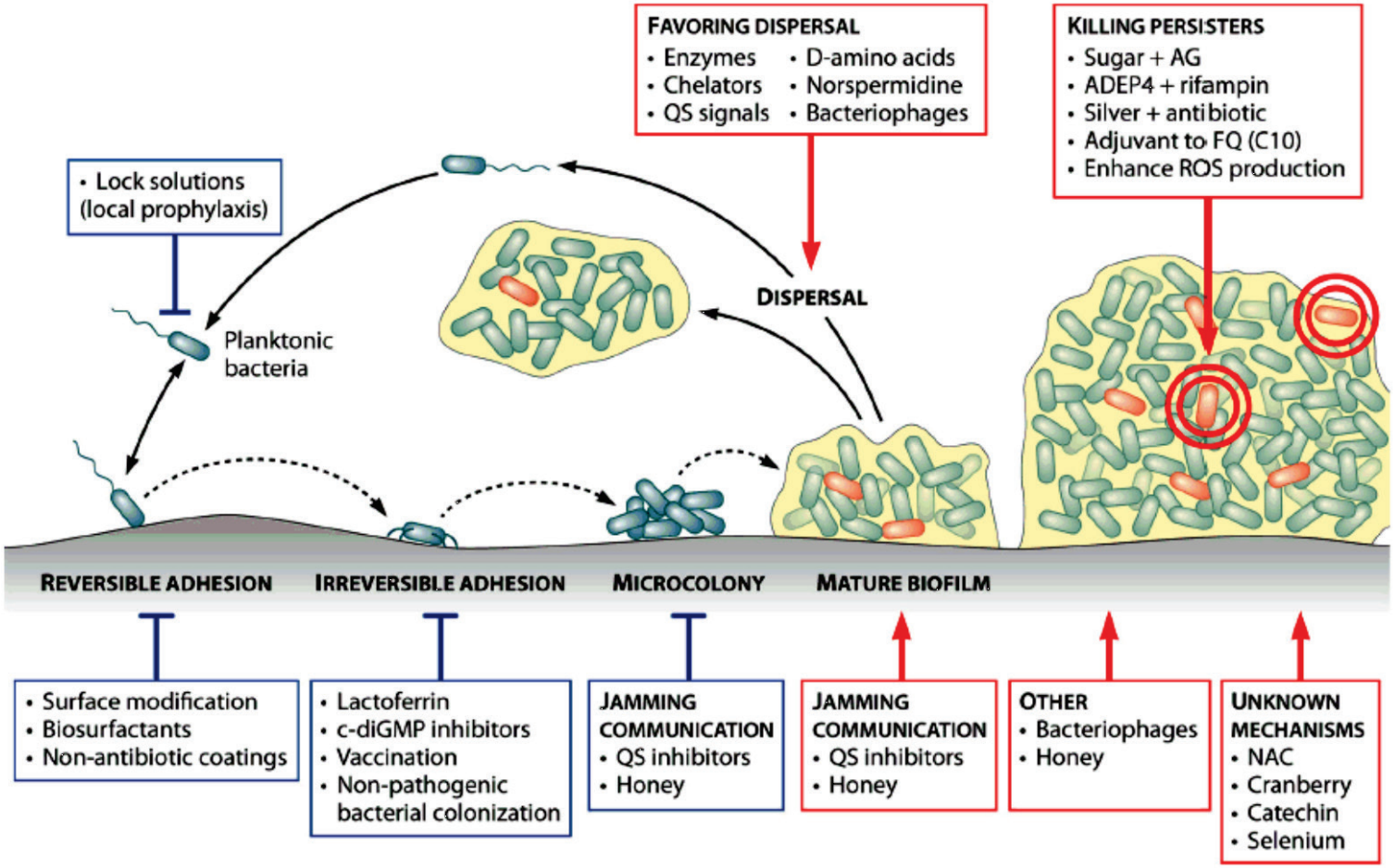


FIG 5 Antibiofilm strategies arising from fundamental research. Approaches to preventing formation of biofilms are depicted in blue; approaches to eradicating an established biofilm are shown in red. Persister cells are shown in red. AG, aminoglycosides; c-diGMP, cyclic di-GMP; FQ, fluoroquinolones; NAC, *N*-acetylcysteine; QS, quorum sensing; ROS, reactive oxygen species.

Lebeaux *et al*. Microb Mol Biol Rev 2014;78:510–543

Will this prevent emergence of resistance ?

ORIGINAL ARTICLE

Reduction of Bacterial Resistance with Inhaled Antibiotics in the Intensive Care Unit

Lucy B. Palmer and Gerald C. Smaldone

Pulmonary, Critical Care and Sleep Division, Department of Medicine, State University of New York at Stony Brook, Stony Brook, New York

Palmer & SmaldoneAm J Respir Crit Care Med Vol 189, Iss 10, pp 1225–1233, May 15, 2014

Will this prevent emergence of resistance ?

ORIGINAL ARTICLE

Reduction of Bact
Intensive Care Un

Lucy B. Palmer and Gerald C.

Pulmonary, Critical Care and Sleep
New York

At a Glance Summary

Scientific Knowledge on the Subject: The intensive care unit is a haven for multidrug-resistant organisms. They frequently arise in the respiratory tract and they are difficult to eradicate. Routine treatment with broad-spectrum systemic antibiotics can lead to further resistance and superinfection.

What This Study Adds to the Field: Inhaled antibiotics can eradicate these organisms and prevent further development of resistance.

Palmer & SmaldoneAm J Respir Crit Care Med Vol 189, Iss 10, pp 1225–1233, May 15, 2014

Will this prevent emergence of resistance ?

ORIGIN

Reduction
Intensive C

Lucy B. Palmer a

Pulmonary, Critical
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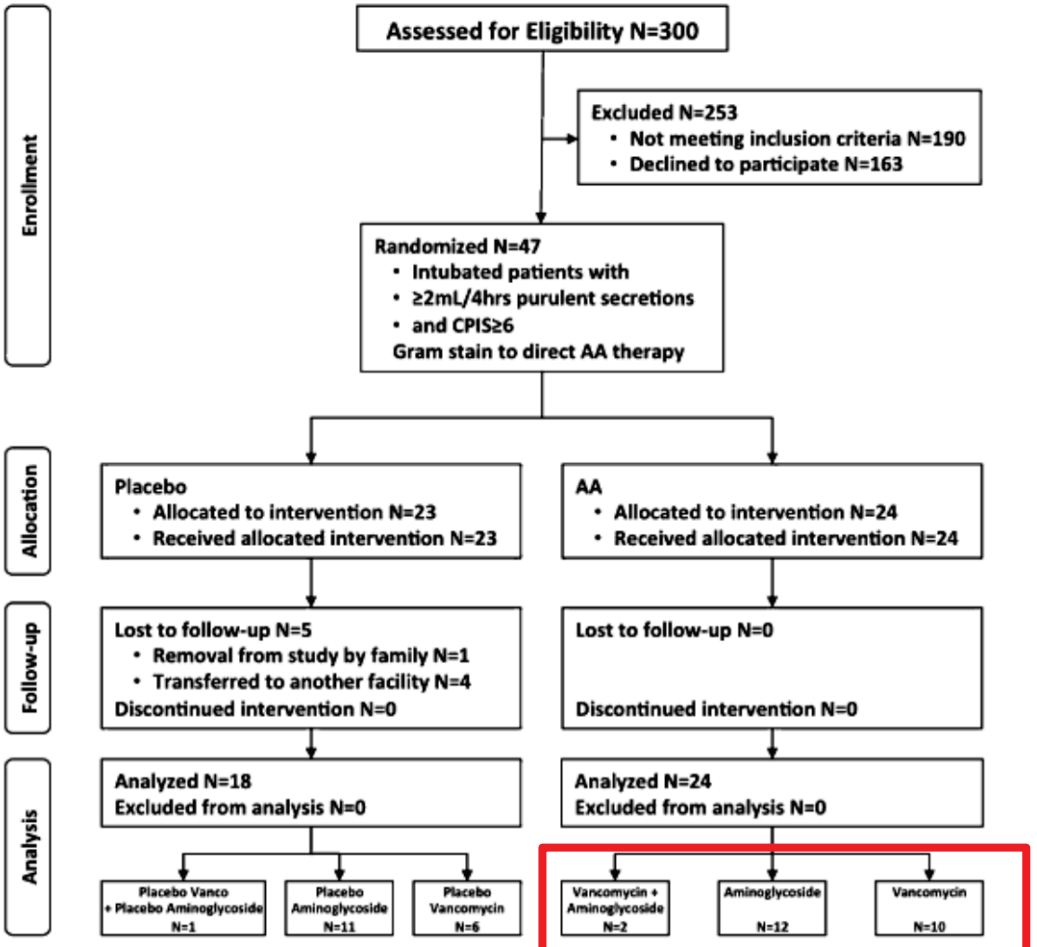

Figure 1. Flow chart for patient recruitment, enrollment, and analysis. AA = aerosolized antibiotics; CPIS = Clinical Pulmonary Infection Score.

Palmer & SmaldoneAm J Respir Crit Care Med Vol 189, Iss 10, pp 1225–1233, May 15, 2014

Will this prevent emergence of resistance ?

Table 5: Systemic Antibiotics and New Resistance during Aerosol Therapy

	Patients with New Resistance during Treatment	Patients	Aerosolized Treatment	Systemic Treatment	Organism
AA (n = 16)	2 (13%)	1	Gentamicin	Piperacillin/tazobactam	VRE
		2	Vancomycin	Cefepime	*Enterobacter* sp.
Placebo (n = 11)	6 (55%)	1	Placebo	Imipenem	PA
		2	Placebo	Imipenem	PA
		3	Placebo	Cefepime, meropenem, vancomycin	*Acinetobacter* sp.
		4	Placebo	Cefepime, gentamicin	PA
		5	Placebo	Vancomycin, piperacillin/tazobactam	*Klebsiella pneumoniae*, MRSA
		6	Placebo	Meropenem, vancomycin	*Enterobacter* sp.
P value*	0.03				

Definition of abbreviations: AA = aerosolized antibiotics; MRSA = methicillin-resistant *staphylococcus aureus*; PA = *Pseudomonas aeruginosa*; VRE = vancomycin-resistant enterococcus.
Data from patients with serial cultures throughout the study.
*Fisher exact test.

Palmer & SmaldoneAm J Respir Crit Care Med Vol 189, Iss 10, pp 1225–1233, May 15, 2014

Will this prevent emergence of resistance ?

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomonas aeruginosa*

Qin Lu[1], Jianxin Yang[2], Zhihai Liu[2], Claudia Gutierrez[3], Guy Aymard[4], Jean-Jacques Rouby[1], and the Nebulized Antibiotics Study Group*

[1]Multidisciplinary Intensive Care Unit Pierre Viars, Department of Anesthesiology and Critical Care Medicine, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France; [2]Department of Emergency Medicine, Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; [3]Department of Anesthesiology, Faculty of Medicine, Federal University of Rio Grande do Sul, Hospital das Clinicas de Porto Alegre, Porto Alegre, Brazil; and [4]Department of Pharmacology, La Pitié-Salpêtrière Hospital, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France

Lu et al. Am J Respir Crit Care Med Vol 184. pp 106–115, 2011

Will this prevent emergence of resistance ?

Nebulized Ceftazidime and Amikacin in Ventilator-associated Pneumonia Caused by *Pseudomo*

Qin Lu[1], Jianxin Yang[2], Zhil
and the Nebulized Antibiotic

[1]Multidisciplinary Intensive Care Ur
Publique-Hôpitaux de Paris, Univer
Zhejiang University School of Med
do Sul, Hospital das Clinicas de Po
Publique-Hôpitaux de Paris, Univer

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In experimental inoculation pneumonia, nebulization of antibiotics provides high lung tissue concentrations and rapid bacterial killing.

What This Study Adds to the Field

Nebulized ceftazidime and amikacin provide clinical cure of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*, including strains with decreased susceptibility to one or both antibiotics, and may prevent per-treatment acquisition of antibiotic resistance.

Assistance
spital,
Rio Grande
istance

Lu et al. Am J Respir Crit Care Med Vol 184. pp 106–115, 2011

TABLE 3. MICROBIOLOGICAL RESPONSE TO TREATMENT AND ANTIBIOTIC SUSCEPTIBILITY OF *PSEUDOMONAS AERUGINOSA* IN EACH GROUP OF PATIENTS

	Baseline	Day 3	Day 5	Day 7	Day 9
Aerosol Group					
BAL, n	20	17	16	12	12
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	1	0	2	5*
CAZ–AMK					
S–S	16	1		2	5
S–I†	1				
I‡–S	2				
I§–I†	1				
Intravenous Group					
BAL, n	20	16	15	10	11
BAL *P. aeruginosa* + *P. aeruginosa* susceptibility, n	20	8	8	5	6
CAZ–AMK					
S–S	17	6	5	1	3
S–I	3	2		1	
I–S			1	2	1
R–S			2	1	1
R–I					1

Definition of abbreviations: AMK = amikacin; BAL = bronchoalveolar lavage; CAZ = ceftazidime; CPIS = modified Clinical Pulmonary Infection Score; I = intermediate; *P. aeruginosa* = *Pseudomonas aeruginosa*; R = resistant; S = susceptible.

The susceptibility of *P. aeruginosa* is defined as follows (36): for ceftazidime, S = minimal inhibitory concentration (MIC) $\geq$ 4 mg·L^{-1}; I = MIC $>$ 4 and $\geq$ 32 mg·L^{-1}; R = MIC $>$ 32 mg·L^{-1}; for amikacin, S = MIC $\geq$ 8 mg·L^{-1}; I = MIC $>$ 8 and $\geq$ 16 mg·L^{-1}; R = MIC $>$16 mg·L^{-1}.

* In two patients, *P. aeruginosa* was identified at concentrations less than 10^3 cfu·ml^{-1}, and there was no evidence of pneumonia recurrence (CPIS $<$ 6 and improvement of lung aeration).

† MIC of amikacin, 16 mg·L^{-1}.

‡ MIC of ceftazidime, 12 and 32 mg·L^{-1}.

§ MIC of ceftazidime, 6 mg·L^{-1}.

Lu et al. Am J Respir Crit Care Med Vol 184. pp 106–115, 2011

Wher are we now ?

CURRENT OPINION

Aerosolized antibiotics: do they add to the treatment of pneumonia?

Marin H. Kollef[a], Cindy W. Hamilton[b,c], and A. Bruce Montgomery[d]

Purpose of review
The increasing rate of ventilator-associated pneumonia (VAP) caused by multidrug-resistant pathogens warrants the development of new treatment strategies. Carefully engineered delivery systems are undergoing evaluation to test the hypothesis that aerosolized administration of antibiotics will provide high local concentrations and fast clearance, which in turn may improve efficacy and decrease the risk of microbial resistance.

Recent findings
Recent studies indicate that aerosolized delivery systems for specially formulated antibiotics yield high local concentrations with rapid clearance and low systemic exposure. Preliminary clinical studies reveal that aerosolized delivery of antibiotics is well tolerated and active, when combined with intravenous antibiotics. No single aerosolized antibiotic is likely to provide broad-spectrum activity against both Gram-negative and Gram-positive bacteria.

Summary
Large multicenter trials are needed to determine whether preliminary findings will translate to improved clinical activity and decreased microbial resistance in VAP patients, and to optimize the use of aerosolized antibiotics.

Kollef et al. Curr Opin Infect Dis 2013, 26:538–544

Will this prevent emergence of resistance ? What are the problems

- Gradient concentrations …
  - **where are the bacteria ?**
  - **where is the antibiotic ?**
- Specific situations in lungs
  - Large inocula
    - heteroresistance / inoculum effects
  - Biofilm formation
    - sharp decrease in susceptibility
    - Dormant/persistent bacteria
  - Intracellular sheltering

Will this prevent e
What ar

- Gradient concentrat
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    - Dormant/persistent b
  - Intracellular shelterir

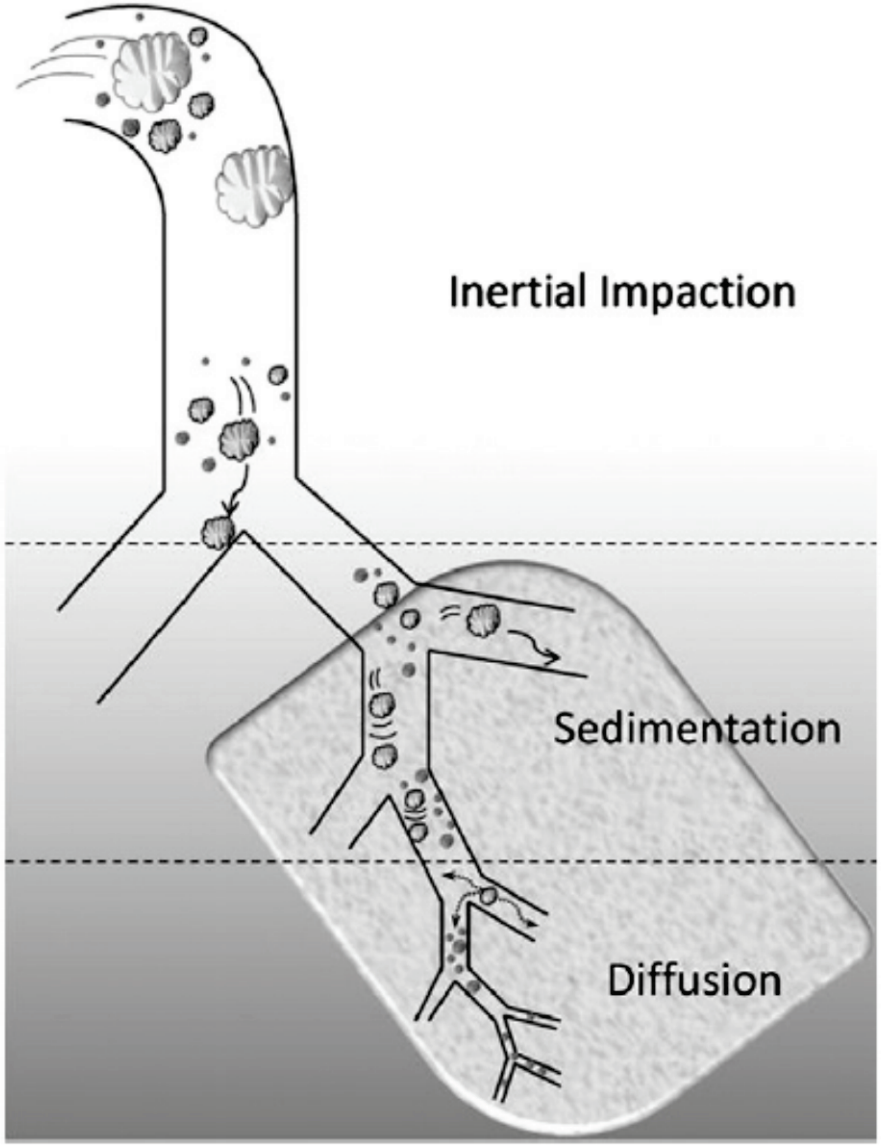

Fig. 2. Mechanisms involved in particle deposition in the different regions of airways. Reproduced from reference [58] with permission of Elsevier.

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Will this prevent emergenc
What are the pro

- Gradient concentrations …
  - **where are the bacteria ?**
  - **where is the antibiotic ?**
- Specific situations in lungs
  - Large inocula
    - heteroresistance / inoculum effects
  - Biofilm formation
    - sharp decrease in susceptibility
    - Dormant/persistent bacteria
  - Intracellular sheltering

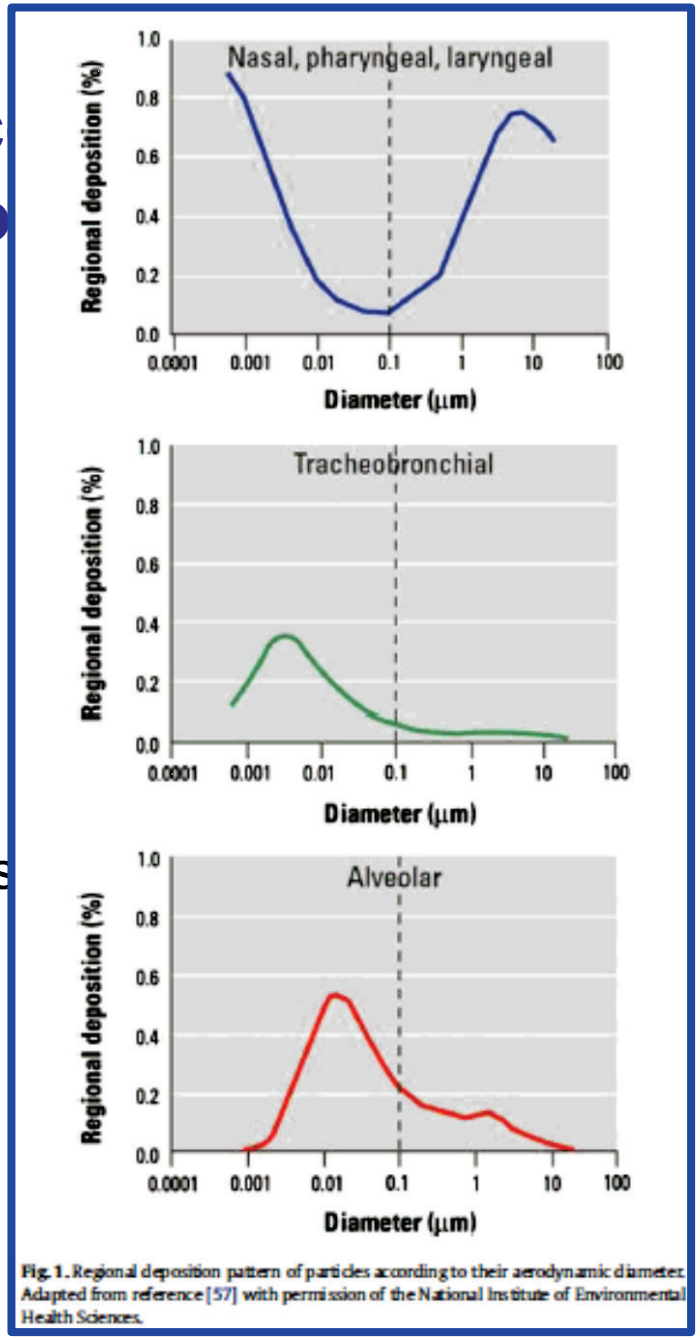

Fig. 1. Regional deposition pattern of particles according to their aerodynamic diameter. Adapted from reference [57] with permission of the National Institute of Environmental Health Sciences.

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Will this prevent emergence of resistance ? What are the problems

- Gradient concentrations …
  - where are the bacteria ?
  - where is the antibiotic ?
- Specific situations in lungs
  - Large inocula
    - heteroresistance / inoculum effects
  - Biofilm formation
    - sharp decrease in susceptibility
    - **Dormant/persistent bacteria**
  - Intracellular sheltering

We may need antipersisters strategies

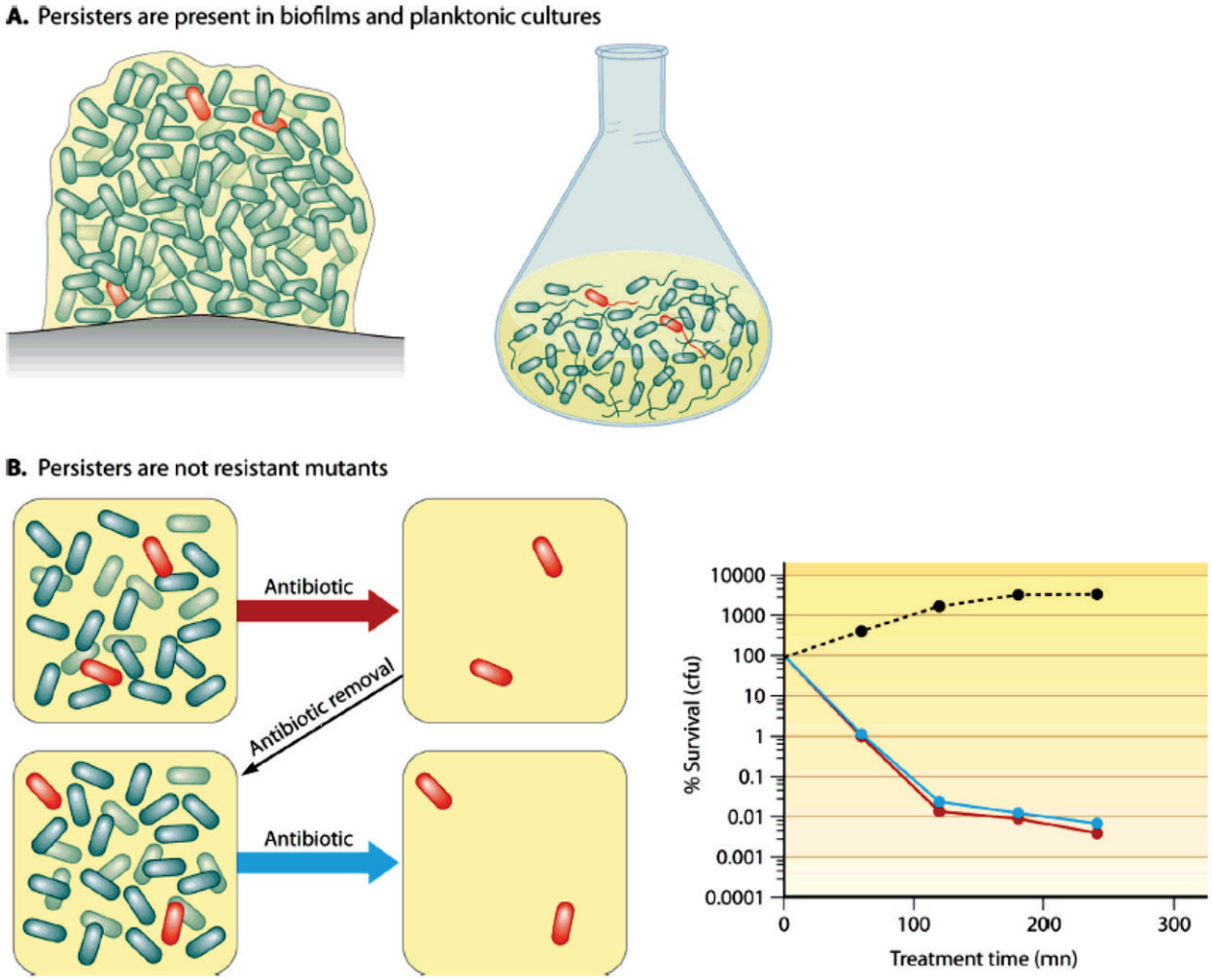

FIG 3 Main phenotypic characteristics of persister cells. (A) Persisters (red bacteria) are present under planktonic and biofilm conditions and account for only a small subset of the whole population (0.001% to 0.1%). (B) Persisters are not resistant mutants. After treatment of a bacterial population with a bactericidal antibiotic, all nonpersister cells die, giving a biphasic survival curve. After a rapid decrease, surviving cell fractions reach a plateau corresponding to persisters (red curve). After antibiotic removal and addition of rich medium, persisters resume growth. The population obtained displays a susceptible phenotype toward the antibiotic (blue curve). If a resistant mutant were present, it would be able to grow in the presence of the antibiotic (dotted line). Panel B was inspired by previous reports (13, 31, 94).

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And some antibiotics may trigger a persistence phenotype

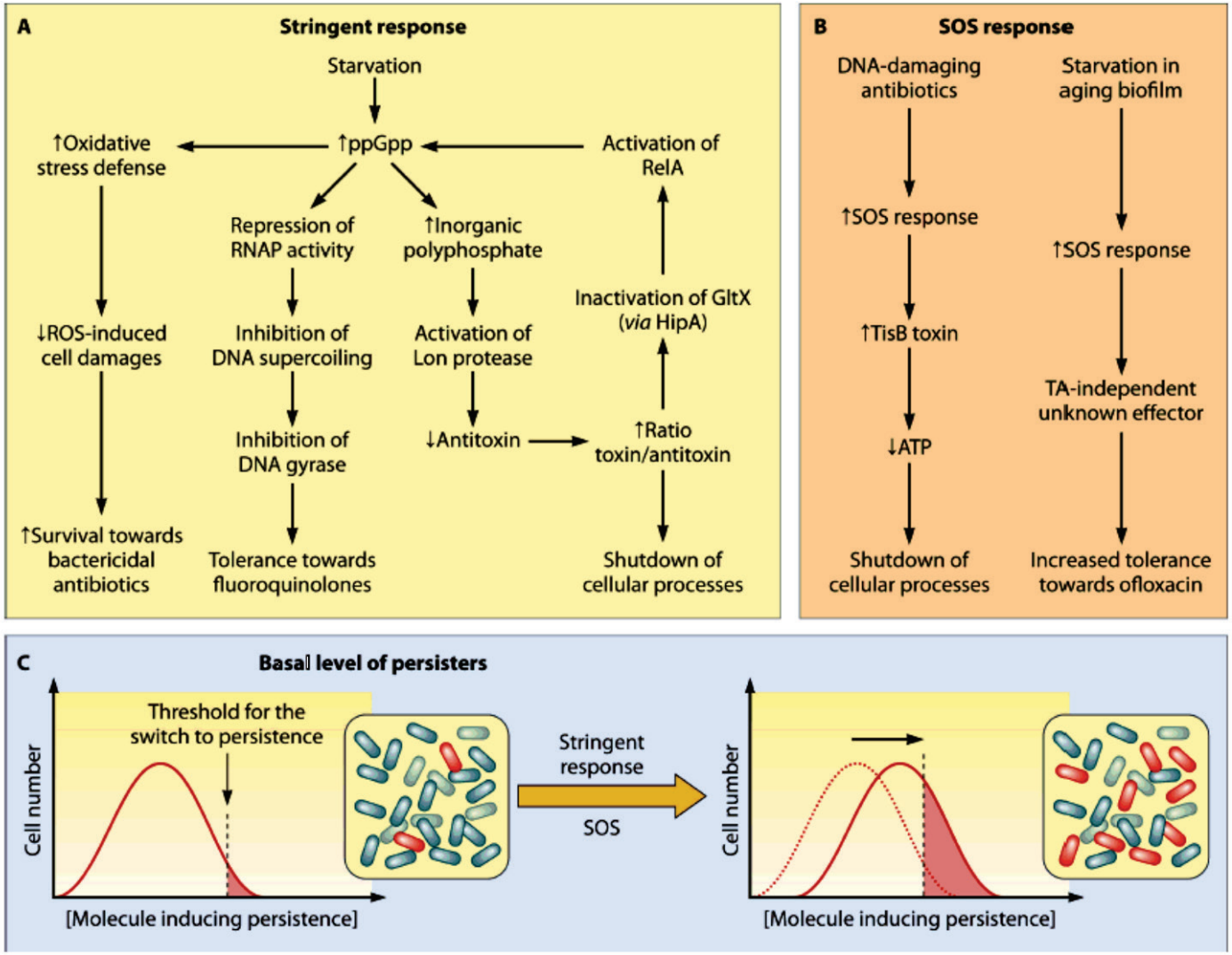

FIG 4 Main factors involved in generation of persisters. The stringent response (A) and the SOS response (B) are now considered pivotal in the generation of persisters. (C) Connection between stochasticity and persister genesis. In exponential-phase cultures, due to stochasticity, only a few bacteria reach the required threshold of a toxic molecule that is necessary to switch to the persister state (in red). Due to the factors described in panels A and B, there is an increased level of molecules inducing persistence; thus, more bacteria reach the threshold and become persisters. Note that most of these studies were conducted with planktonic bacteria. Panel C was inspired by a previous report (103).

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And here is the team …

The boss !

The biofilm Experts !

The persisters guy !

The cystic fibrosis fellow

The inhalation guy !

The intracellular infection experts

See them all on http://www.facm.ucl.ac.be

Thank you for your attention!

And ask questions