

*Cystic fibrosis -
Early eradication therapy
against *Pseudomonas a.**

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UCL, Brussels, march 2006

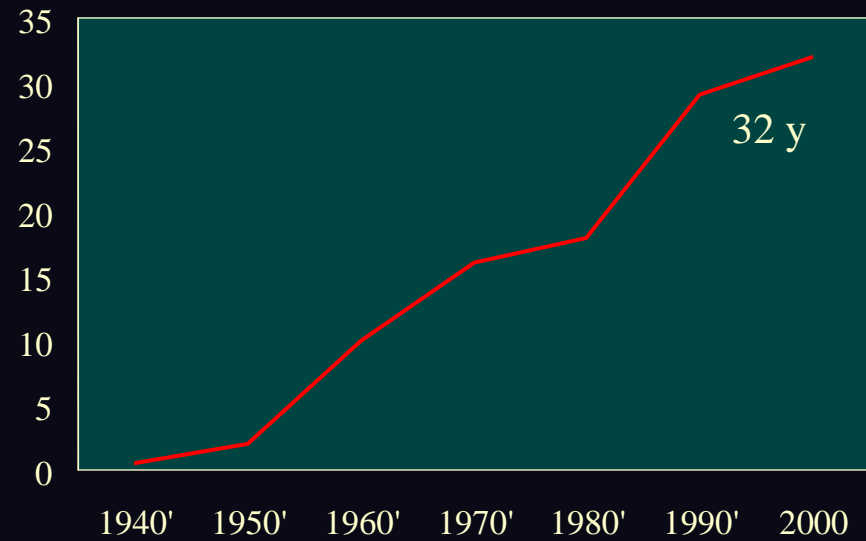
- Introduction
- Chronic colonization by Ps a :
 - steps
 - definition
 - consequences
- Current concept : the window of opportunity
- Early intervention :
 - modalities
 - pitfalls
- Prophylaxis ?

Introduction

- increased life expectancy

USA

Median life expectancy (y)



- > 18 y

USA 2004 : 41.8 %

Belgium 2003 : 44 %

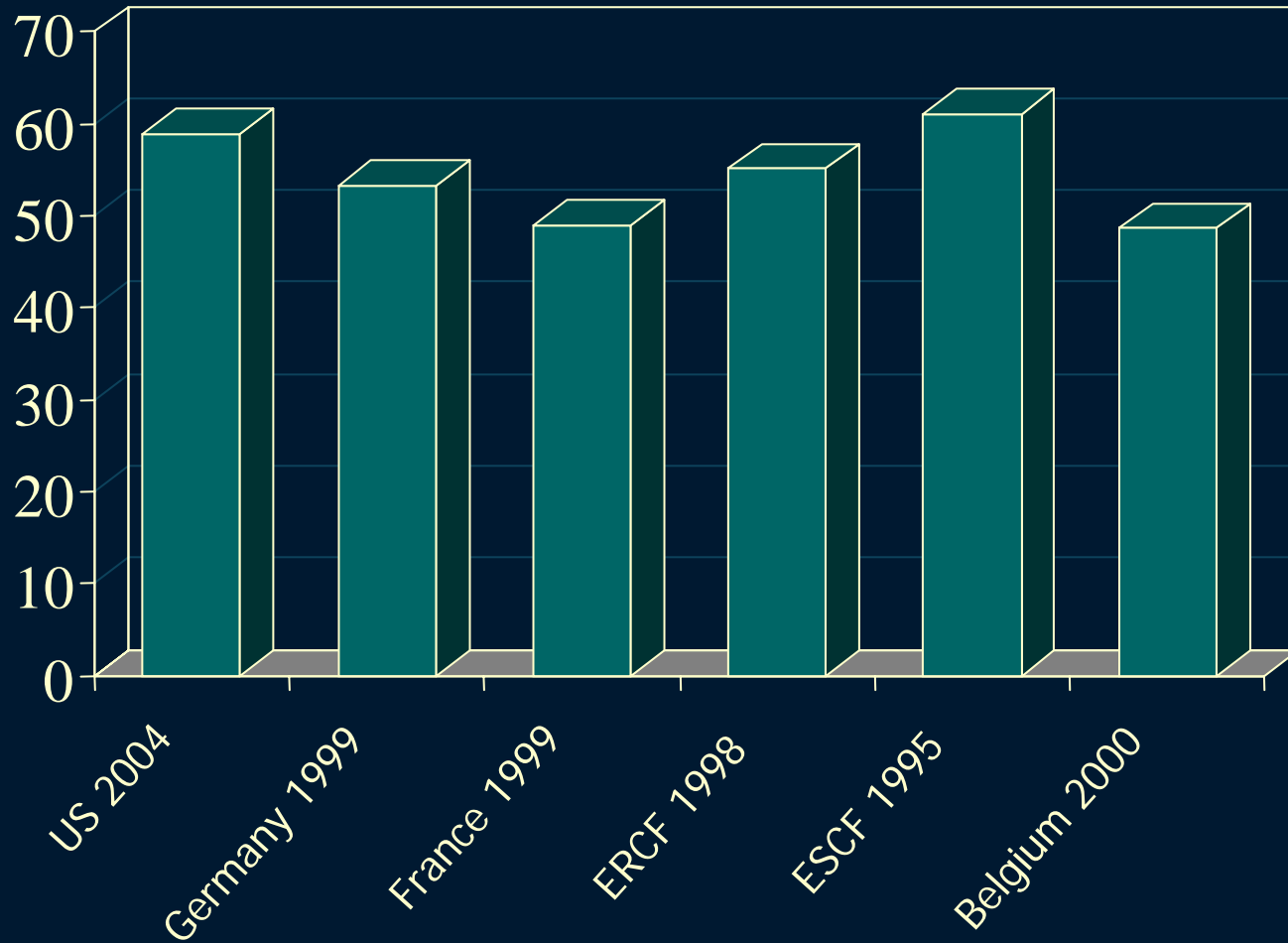
Introduction

- increased life expectancy
- AB therapy considered essential

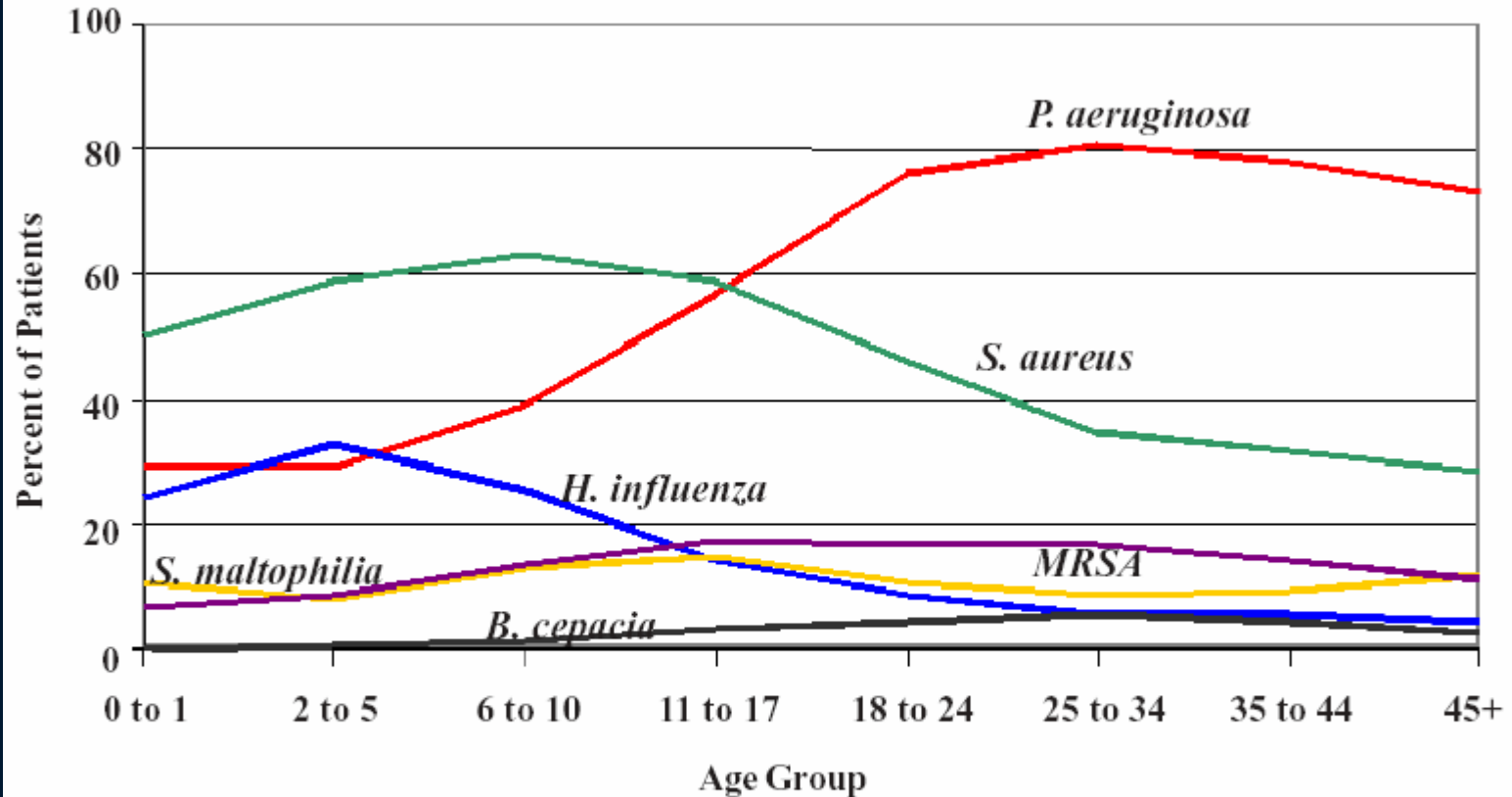
Introduction

- increased life expectancy
- AB therapy considered essential
- Ps a prevalence

- *Ps a.* Prevalence



Respiratory Infections vs. Age



Overall Percentage in 2004:

- *P. aeruginosa* 57.3%
- *S. aureus* 51.7%
- *H. influenzae* 16.2%
- *S. maltophilia* 11.6%
- *B. cepacia* complex 2.9%
- *MRSA* 14.6%

Chronic colonization by *Ps a*

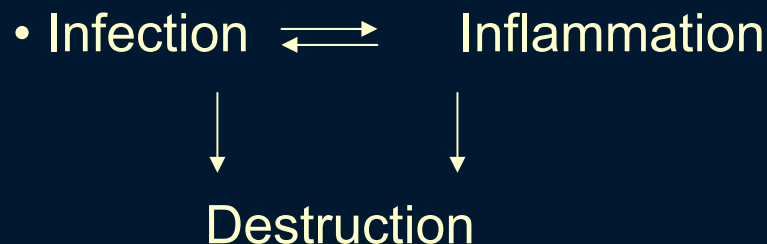
- steps
- definition
- consequences

- route : nose, mouth ?
- peculiar interaction with CF lung epithelium : ??

Small airways

Baltimore Am Rev Respir Dis 1989 140: 1650-61

- non mucoid → mucoid
exopolysaccharide (alginate)-coated microcolonies (biofilm)
 - more resistance against phagocytosis
 - poor penetration of AB
- type III hypersensitivity reaction
specific antibodies immune-complexes
large number of neutrophils (→ proteinases)



*Chronic colonization by *Ps a**

- steps
- definition
- consequences

- European consensus

Presence of Pa in the bronchial tree for at least 6 months, based on at least 3 positive cultures with at least one month in between by intervals between them

without direct (inflammation, fever ...) or indirect (specific antibody response) signs of infection and tissue damage.

Doring Eur Respir J 2000 16:749-67

- Lee's classification

Monthly *P. aeruginosa* Culture Status

Patients were defined each successive calendar month as:

- 1) *P. aeruginosa* culture-positive (one or more *P. aeruginosa*-positive cough swabs or sputum cultures that month);
- 2) *P. aeruginosa* culture-negative (all cough swabs or sputum cultures that month negative for *P. aeruginosa*); or
- 3) No cough swab or sputum culture performed that month.

P. aeruginosa Infection Category

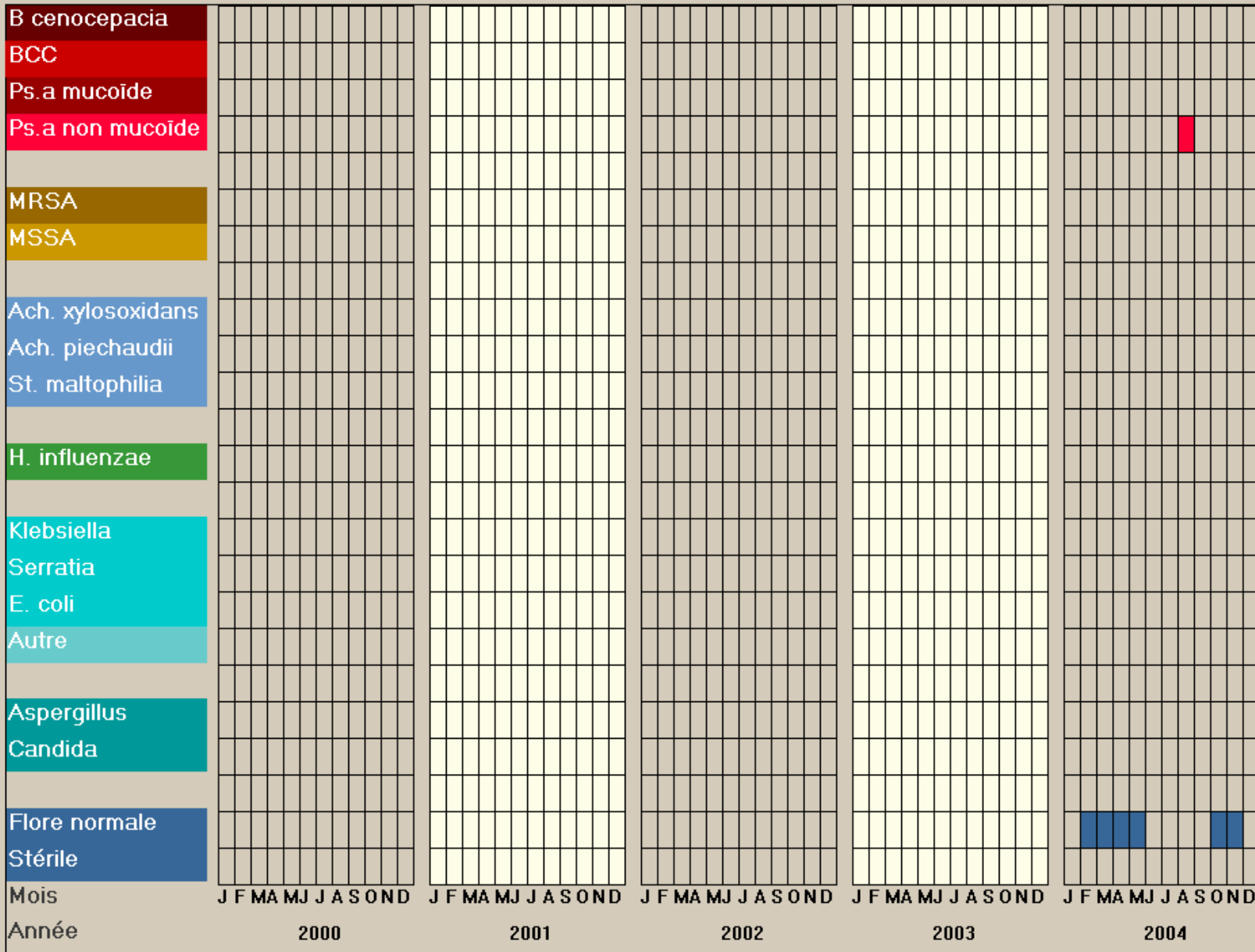
All patients in the clinic were categorized each successive month according to their *P. aeruginosa* culture status over the preceding 12 calendar months on the following basis:

Chronic: Chronic *P. aeruginosa* infection, with more than 50% of months when samples had been taken being *P. aeruginosa* culture-positive.

Intermittent: Intermittent *P. aeruginosa* colonization, with 50% or less of months when samples had been taken being *P. aeruginosa* culture-positive.

Free: Free of *P. aeruginosa*, with no growth of *P. aeruginosa* for the previous 12 months, having previously been *P. aeruginosa* culture-positive.

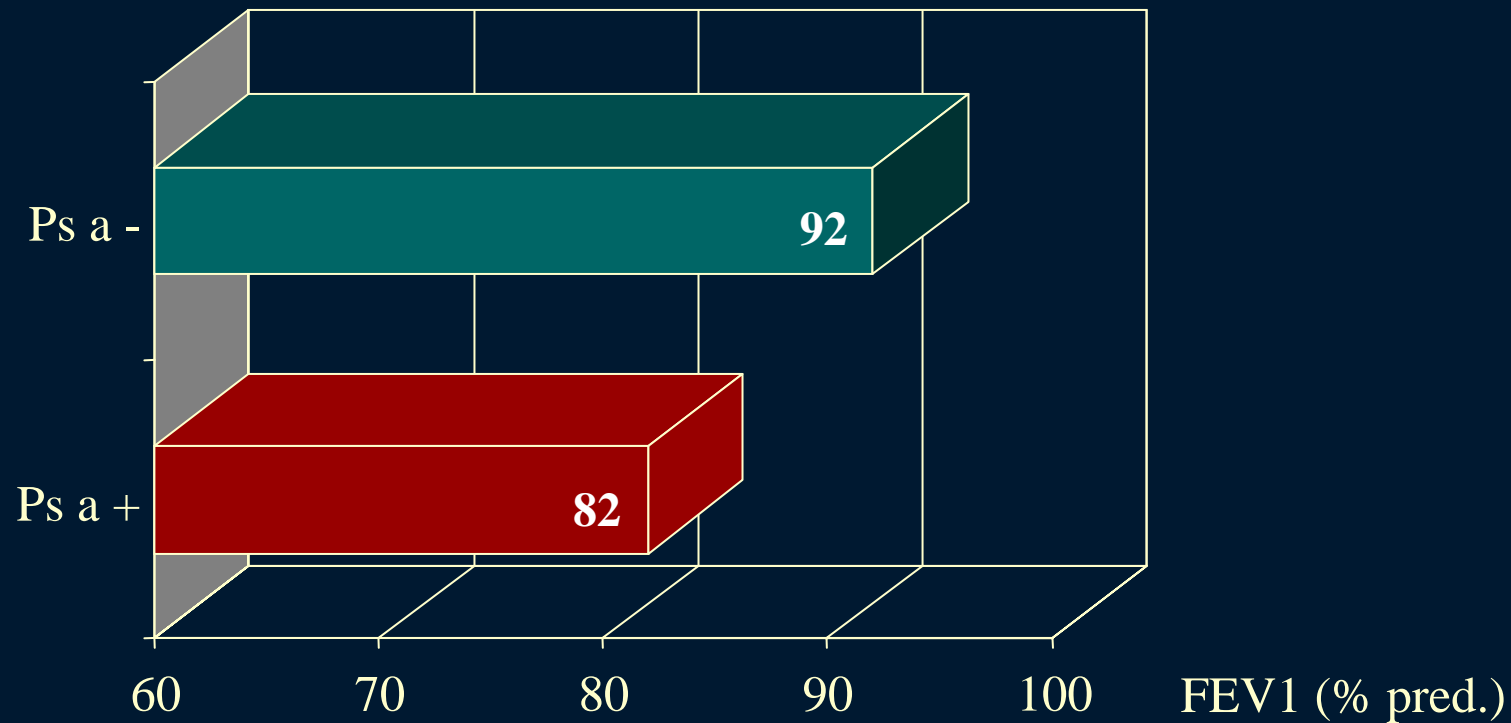
Never: Never grown *P. aeruginosa*.



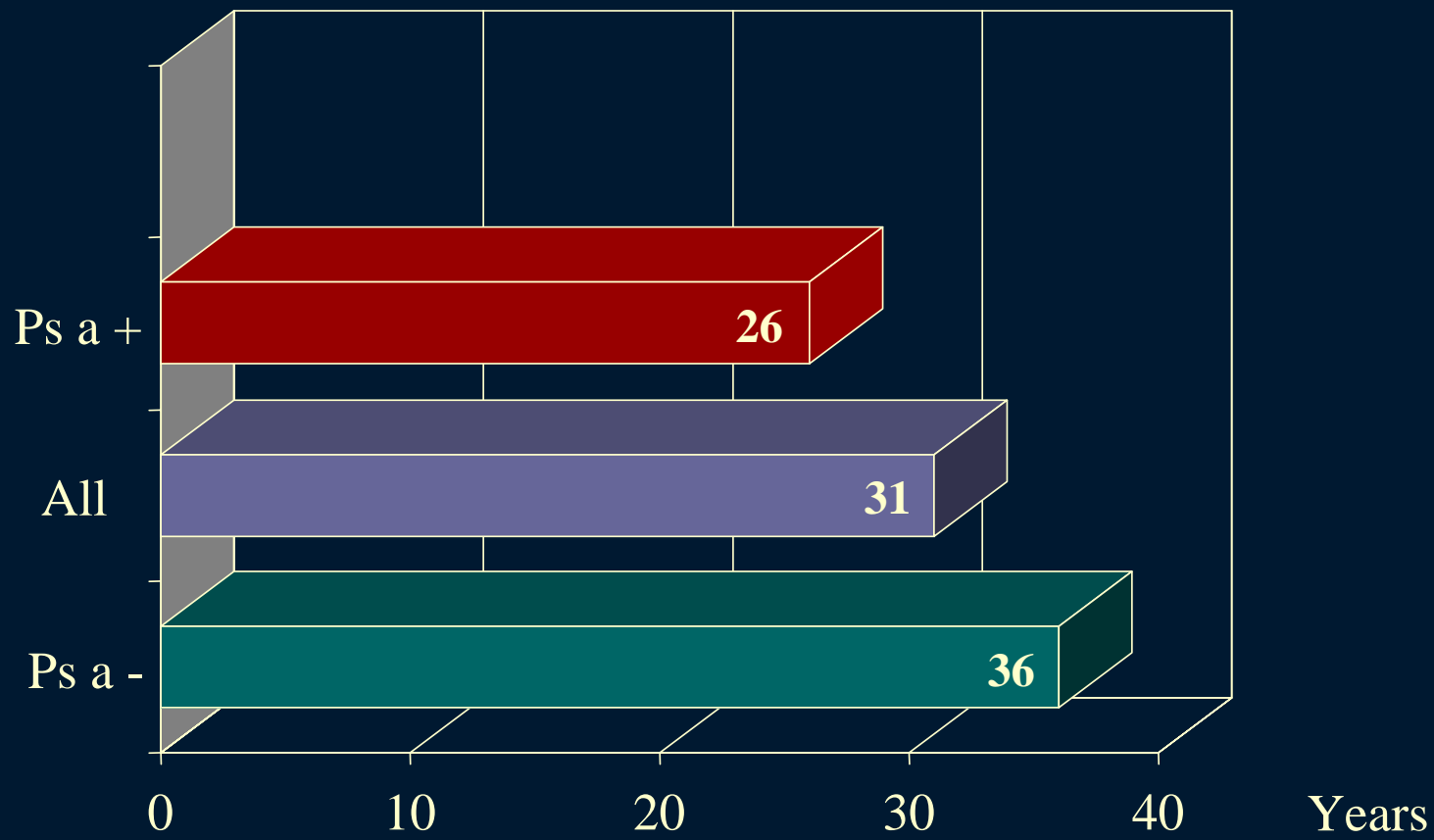
*Chronic colonization by *Ps a**

- steps
- definition
- consequences

- *Ps.a* & FEV1 by the age of 7 years

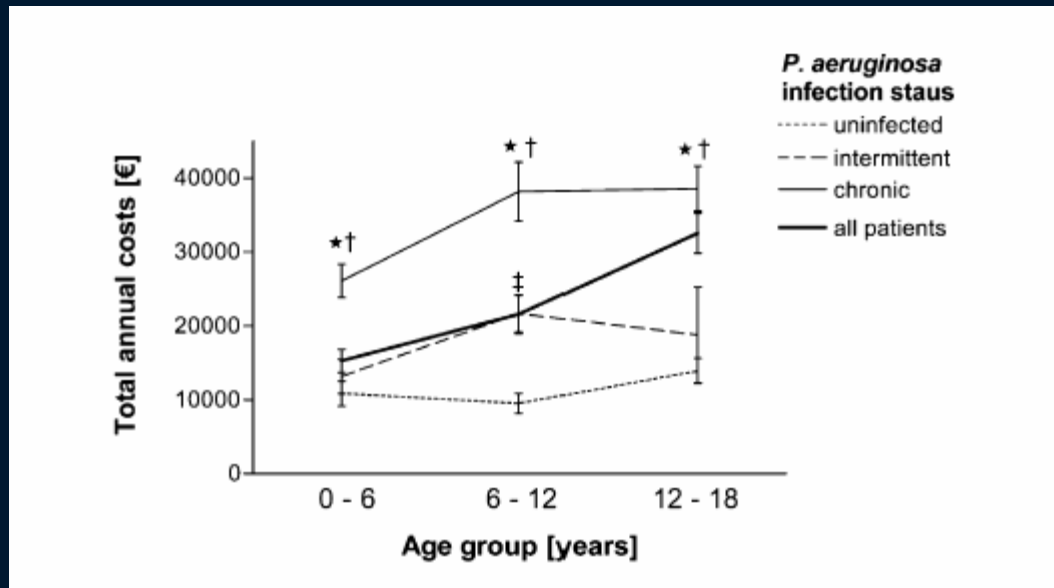


- *Ps.a* & Median life expectancy



CFF, Patient Registry 1995

- *Ps.a* & Cost of treatment



Baumann J Cyst Fibros 2003 2: 84-90

**ANTIBIOTIC TREATMENT
FOR CYSTIC FIBROSIS**

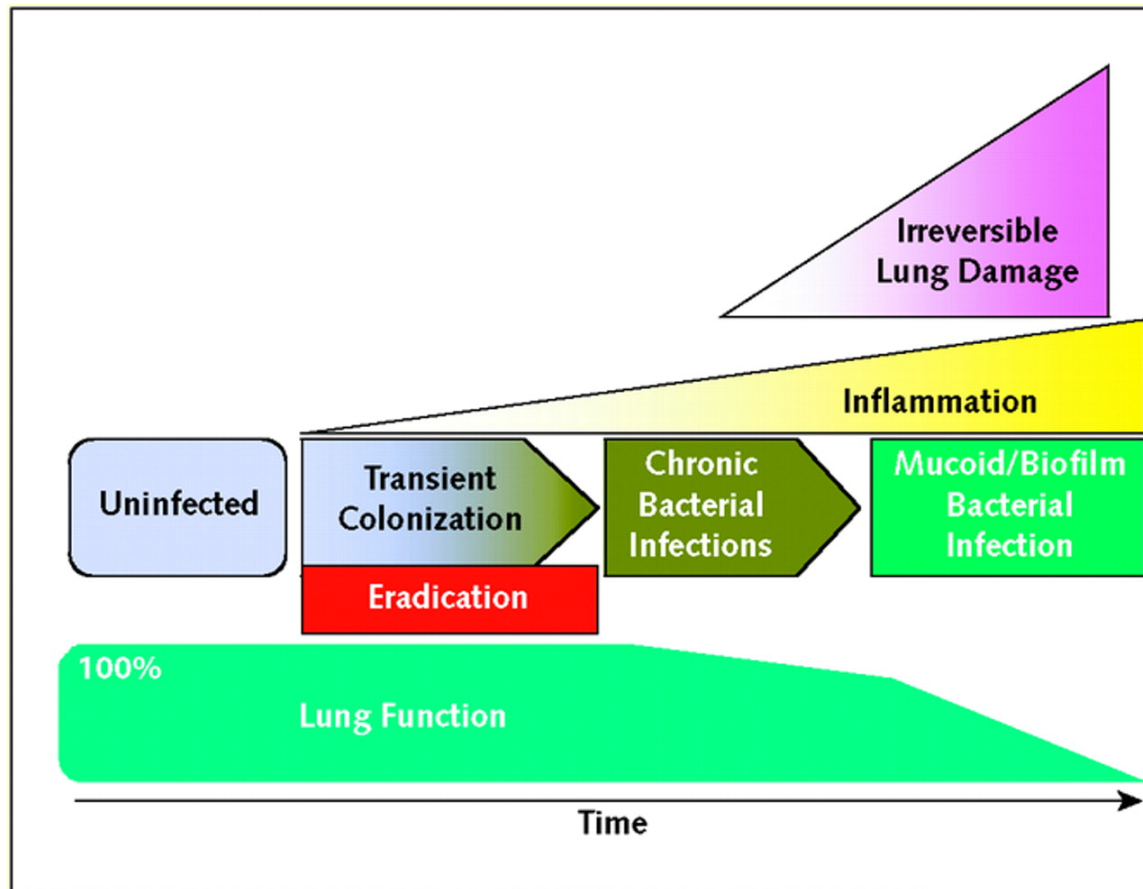


**Report of the
UK Cystic Fibrosis Trust
Antibiotic Group**

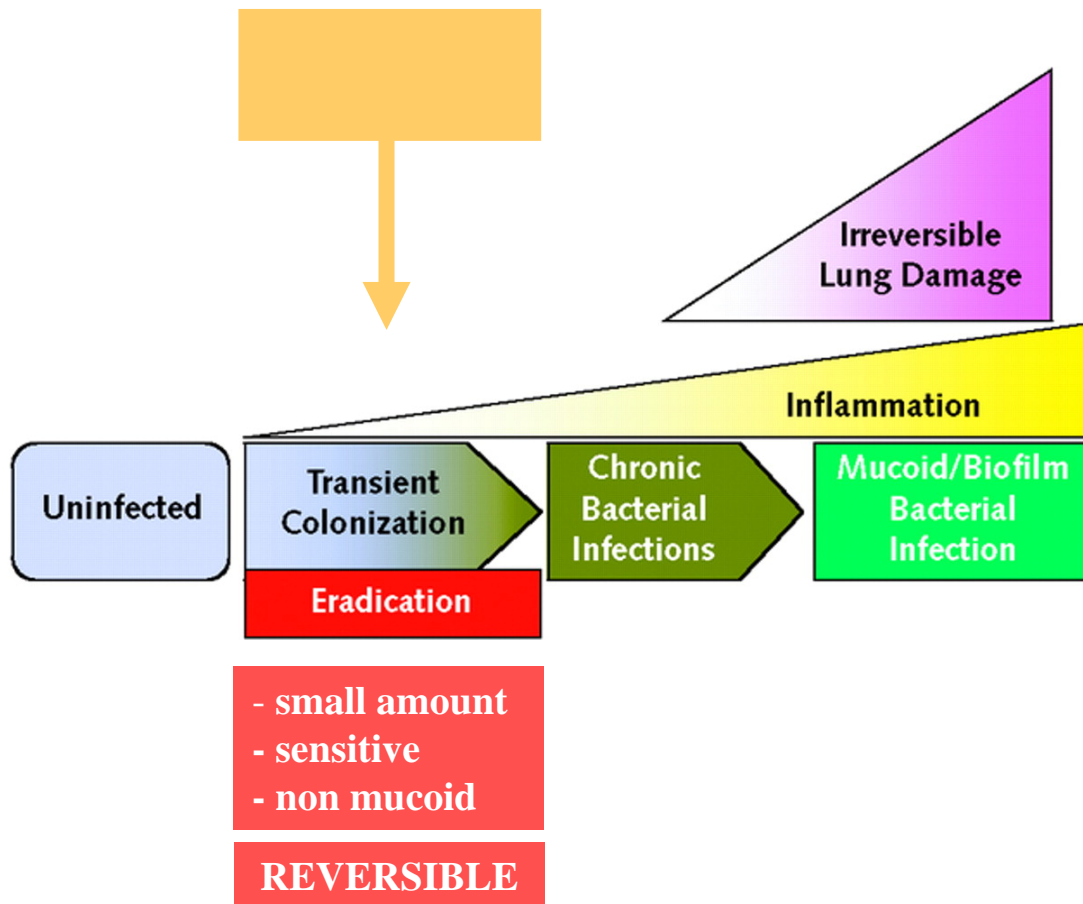
September 2002

The quality of life, length of survival and the cost of care are commonly determined by the success or otherwise of the antibiotic treatment of the initial *P. aeruginosa* infection in early childhood, and by the subsequent antibiotic treatment.

Ps aeruginosa : the window of opportunity



Ps aeruginosa : the window of opportunity



Early intervention : modalities

- No clear consensus
 - route
 - medications
 - duration
- Inhaled colistin + oral ciprofloxacin for 3 months ?

Study	RCT	Treatment	Duration	Success (n)	Success (%)	Duration of eradication
Littlewood 1985	-	Colistin	3-14 m	NA	NA	Not studied
Valerius 1991	+	Cipro + Colistin	3w	12/14 vs 5/12	86%	Not studied
Fredericksen 1997	-	Cipro + Colistin	3w or 3 m	41/48 vs 24/43	85%	Not studied
Wiesemann 1998	+	Inh Tobra 80 mg BID	12 m	8/9 vs 1/4	89%	Not studied
Munck 2001	-	IV AB then colistin	21 d → 2 m	19/19	100	8 ± 6 m
Ratjen 2001	-	Inh Tobra 80 mg BID	12 m	14/15	93	14/15 > 12 m
Nixon 2001	-	IV AB then Cipro	14 d → 3 m	Not studied		6/24 > 12 m
Griese 2002	-	<5 : inh Tobra >5: Cipro + colistin	28 d 3 w	7/8 6/8	88 67	> 2 y
Gibson 2003	+	TOBI 300 mg BID	28 d	8/8 vs 1/13	100%	Not studied
Lee 2004	-	Cipro + Colistin	3 m	23/31	74%	Not studied
Tacetti 2005	-	Cipro + Colistin	3w to 3 m	47/58	81%	50% < 18 m cost effective
11 (1985-2005)	3 RCT	Cipro & Colistin ...	3w → 1 y	3/11 > 30	± 85%	1x PA = ↑ risk for PA reacq.

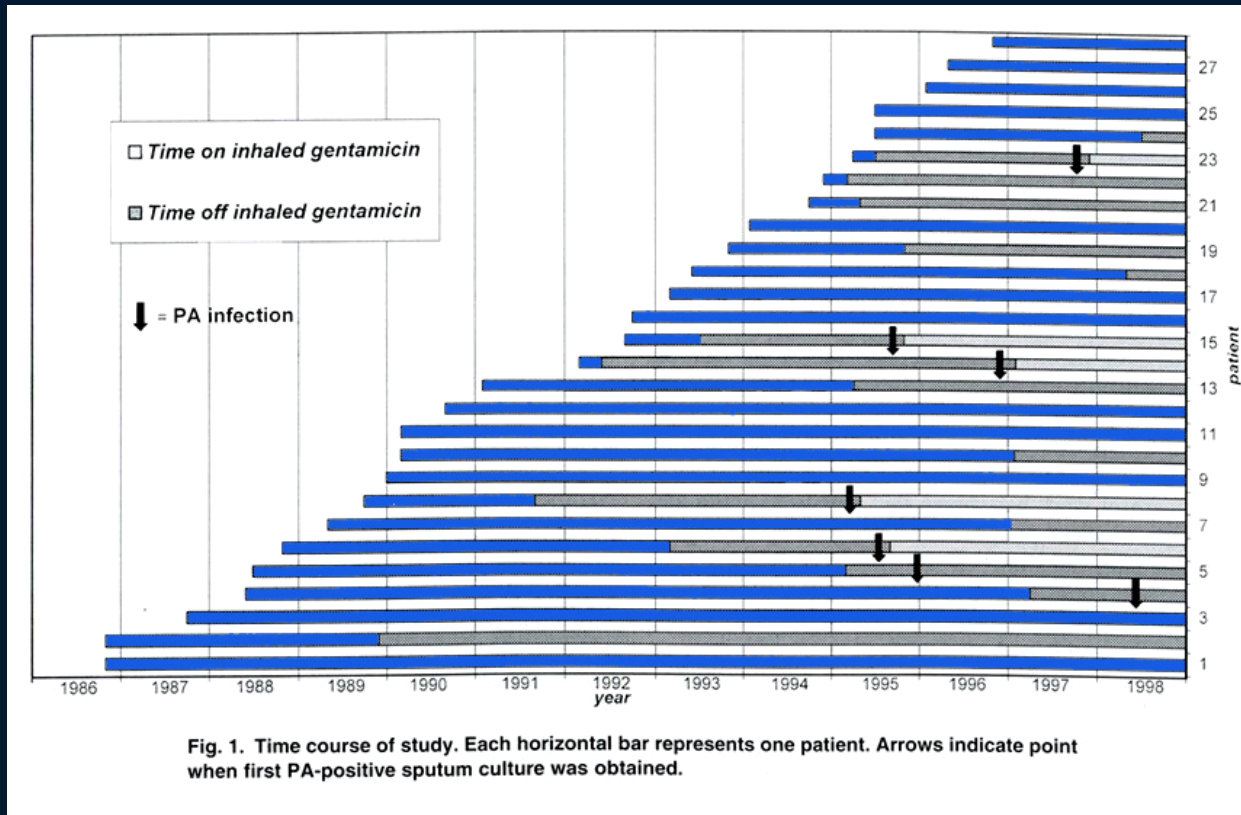
Early intervention : pitfalls

- Which sample ?
- At which frequency ?
- Cultures sensitive enough ? (PCR ? PA antibodies)
- Failure rate of early intervention : 15-20 %

Early inhaled AB ?

- Better penetration
- Effectiveness against other common pathogens in CF (aminoglycosides)
- Safety

- Prophylactic use of inhaled AB ?



132 years without any acquisition of *Ps a* ...

- Risk factors for acquisition of Ps a

- + Early diagnosis
- + Meconium ileus
- + Admission to an intensive care unit
- + Hospital stays
- + Center effect
- + Exposure to patients Ps +
- + Female gender
- + Aerosol use
- + Homozygous $\Delta F508$ genotype
- + More frequent positive *St a* cultures
- + Long-term anti-staphylococcal prophylaxis
- + Viral infections, especially early in life
- Increased mother's education
- PS

Maselli 2003

Stutman 2002

Wang 2001

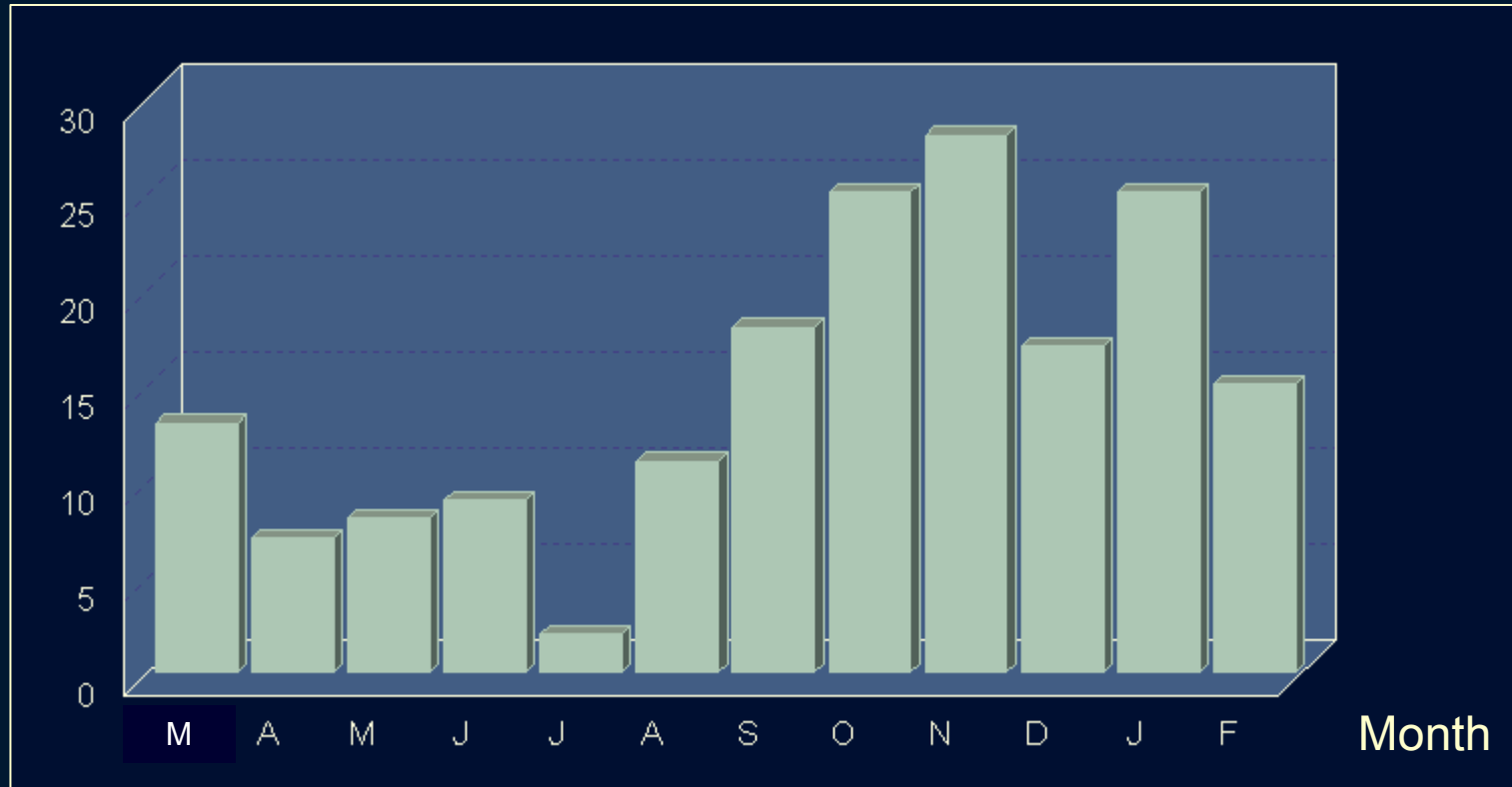
Kosorok 1998

Kubesch 1993

Johansen 1992

Kerem 1990

Initial Ps a colonisation



Johansen Thorax 1992; 47:109-11

St Luc
CF children
Prophylactic inhaled AB

	2003 St Luc	2003 6 main B centres	2003 B Registry	2003 CFF	2005 St Luc
PA prevalence	5%	24% (5-46)			
PA chronic colonization	2/72				1/81
Mean FEV1 (% pr)	95	85 (74-95)			98
FEV1 ≥ 90% pr (%)	70		52	45.2	72
Mean WFH (%) ± SD	100	95 (88-100)			104
IV AB days / child	1,34		5,15		