ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

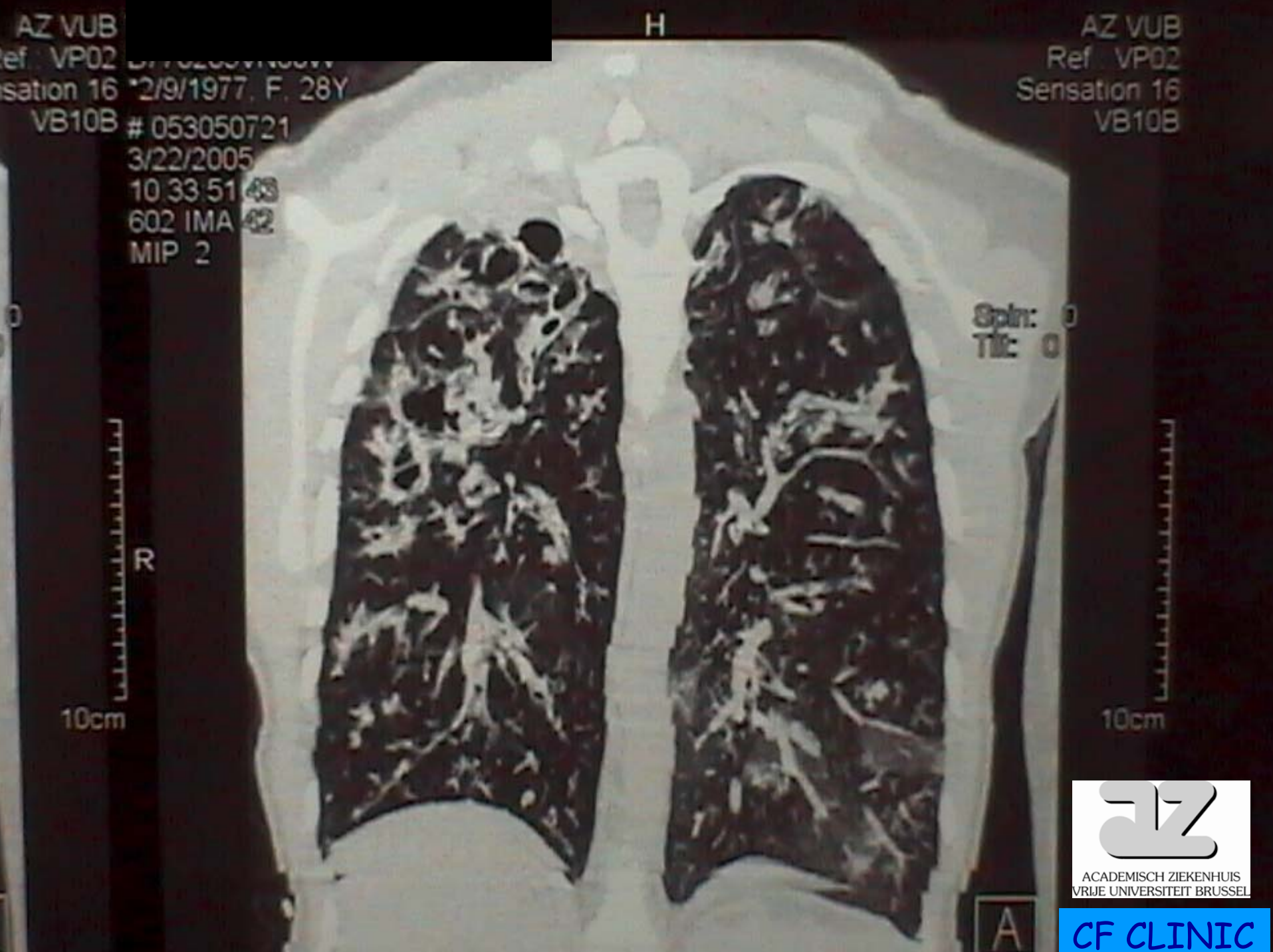
CF CLINIC

Pseudomonas aeruginosa: therapeutic options in Cystic Fibrosis patients

Anne Malfroot, MD,PhD

CF Clinic

AZ-VUB, Brussels



ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Identifying Pulmonary Infection:
obtaining respiratory tract specimens

sputum expectorating patients >> 5 years

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Identifying Pulmonary Infection:
obtaining respiratory tract specimens

- < 5 years: non-sputum producers
  - (induced sputum after hypertonic saline inhalation : > 5 years)
  - oropharyngeal (OP) or “cough” swabs
  - bronchoalveolar lavage (BAL)

  - ⇔ controversy

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

obtaining respiratory tract specimens: oropharyngeal (OP) swabs

-lung physiotherapy -> deep throat culture or suction

-OP swabs more accurate in CF

-false+ (ENT) => "over-treatment" => ↑ resistance

-false- =>

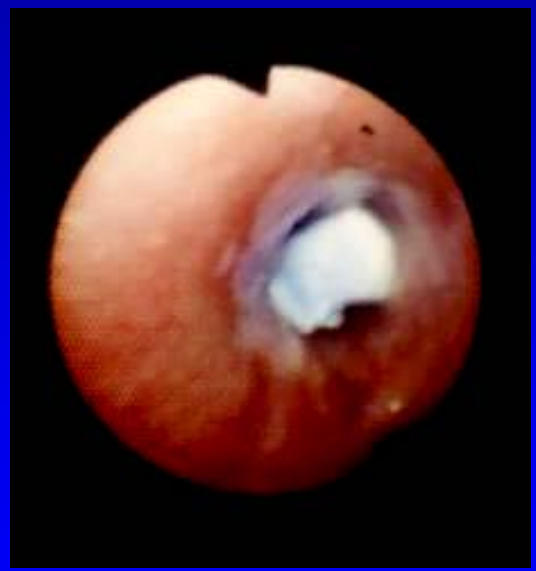
} -> use of serum *Pa* Ab

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

obtaining respiratory tract specimens:bronchoalveolar lavage (BAL)

- advantages: golden standard for lower aw (Jung. ERJ 2002)
  - Burns (JID 2001): PA +: 18% (1y) -> 33% (3y)
  - therapeutic role



- disadvantages: invasive, sedation, limitated use

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

oral insertion

Grigg. J Pediatr 1993

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Laboratory aspects:
questions of the clinician

- Cultures 4x/y + at every clinical suspicion
- Relevance direct examination (gram staining ?)
- Relevance semi-quantitative cultures
- Culture frequency during therapy

  - Miller. J Clin Micrbiol 2003
  - Döring. ERJ 2000
  - Lauwers. Az-VUB consensus 2004

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Identifying Pulmonary Infection:
obtaining respiratory tract specimens
OP versus BAL in CF < 5 years

- OP: **high** specificity & negative predictive value <-> **low** sensitivity & positive predictive value
- BAL: golden standard -> if + OP for PA should be confirmed by BAL

(comparative studies: Armstrong Ped Pulm 1996, Ramsey Am Rev Respir Dis 1991, Wainwright Ped Pulm 2002)

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL
CF CLINIC

Antibiotic strategies against *Pa*: goals

- aggressive treatment of initial isolation (non-mucoid)
- eradication (virtually impossible in mucoid strains and chronic infection state)
- reduction of *Pa* colony counts – temporal undetectability of *Pa* – temporal eradication
- maintain or improve pulmonary function in colonized/infected CF patients
- avoid chronic infection state with AB resistant strains -> pulmonary deterioration -> mortality
    - Döring. ERJ 2000

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Antibiotic strategies against *Pa*: emergence of resistance

- remove selective AB pressure
- susceptible organisms (non-mucoid) will overgrow resistant forms at the end of treatment
- frequent changing from one antibiotic to another
- avoid prolonged monotherapy (<-> controverse: inhaled colistin)
- even resistant strains can lead to a treatment (repeated) response
    - Döring. ERJ 2000

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL
CF CLINIC

Definitions
(adapted from Döring et al. ERJ 2000)

- 1. Resp *Pa* colonization: presence of *Pa* without inflammation
- 2. Chronic *Pa* colonization: presence of *Pa* 3x/6 months –1 m interval
- 3. Resp infection: inflammation, fever, serum Ab (even with – cultures)
- 4. Chron resp infection: 2 + 3

Definitions
(adapted from Döring et al. ERJ 2000)

- Maintenance antibiotic therapy: prolonged, continuous or intermittent antibiotic therapy, even in absence of acute exacerbation
- Prophylactic antibiotic therapy: before detection of *Pa* (to prevent colonization)
- Antibiotic therapy at first isolation of *Pa*
- Antibiotic therapy on demand: only at acute exacerbation
- Antibiotic therapy 4x/year

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL
CF CLINIC

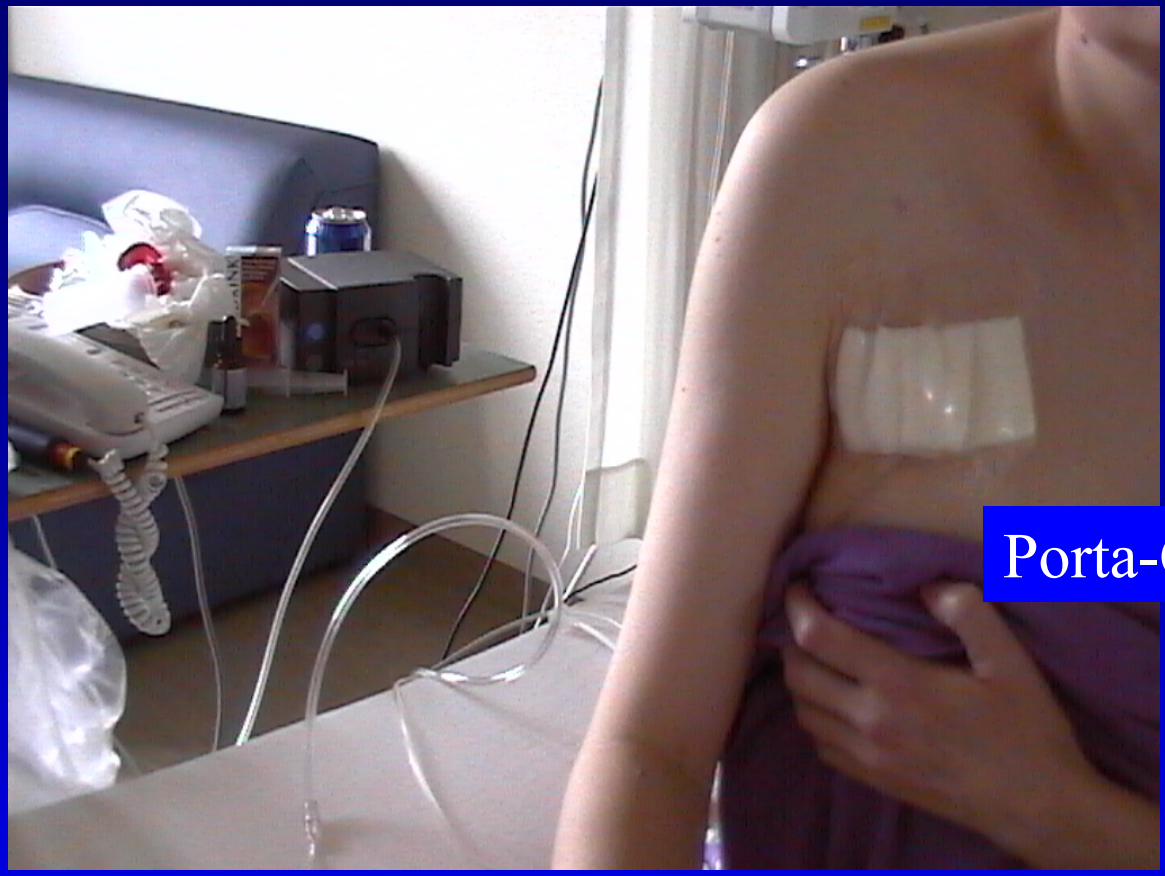
Therapeutic options: routes

- intravenous antibiotic therapy (Porta-Cath)
- oral antibiotic therapy
- nebulized antibiotic therapy
- home intravenous antibiotic therapy
- chronic oral azithromycin association (3d/w -> alginate mucoid *Pa*)

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL



Duration IV treatment: 10d – 3 weeks or >>> (individualized)

AB choice combination according to sensitivity testing

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Antibiotic treatment (doses in CF)

CF CLINIC

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

AB	dose/kg BW per day	adult dose	max dose
amikacin	24mg/kg in 2x	id	* RI
tobramycin	10mg/kg in 2x	id	* RI
colimycin	75000U/kg in 3x	$3x10^6$ U/d	6.10^6 U/d
ciprofloxacin	IV: 20-30mg/kg in 3x OR: 30-40mg/kg in 2x	IV: 2-3x400mg OR:2x750mg	 2x1g
aztreonam	200mg/kg in 4x cont 100mg/kg	4x2g cont16mg/kg-> 8g/24h	12g
ceftazidime	200mg/kg in 4x cont 100mg/kg	4x2g cont15mg/kg-> 6g/24h	12g
meropenem	120mg/kg in 3x	3x2g	6g
temocillin	50mg/kg in 2x	2x2g	6g (>>*Bm*)
pip/tazobactam	300mg/kg in 3x	4x4g	24g

Intravenous treatment (toxicity of aminoglycosides)

- Non-oliguric RI, rise in serum creatinine
- Ototoxicity
- => individual tailoring doses (each course)
- => check-up renal, audiology (at least annual)
- Be aware of individualized pharmacokinetics !!!

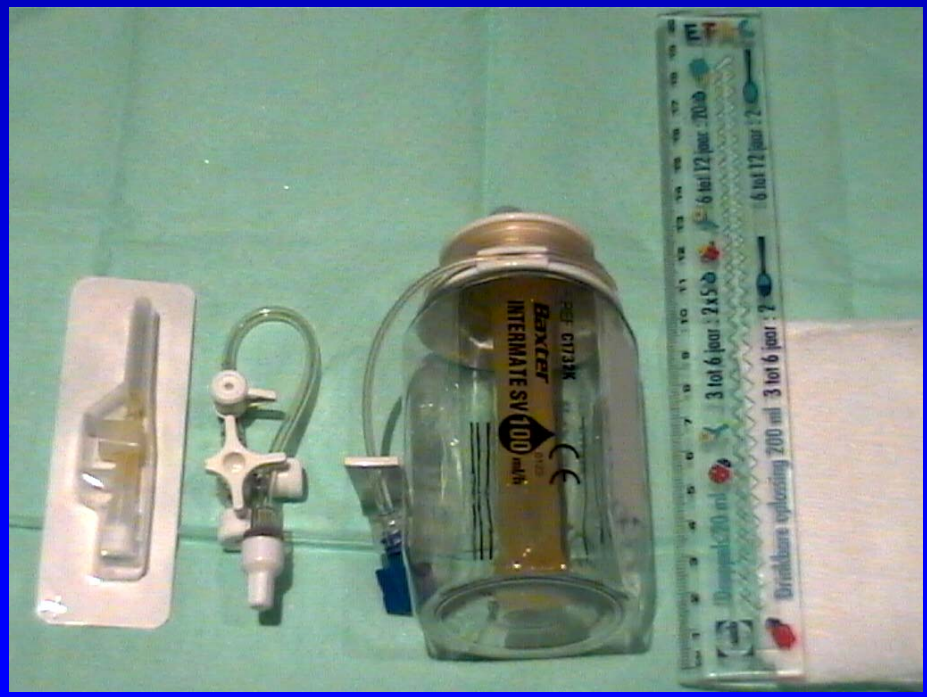
Intravenous treatment (ambulatory)

use of portable elastomeric pumps, battery –less, disposable

uses elastomeric pressure for continuous drug delivery

spec fill volumes (60-300ml) & spec delivery times (30min-7 days)

disadvantages: price!!!, 1 AB/ pump – no mixing of drugs



CF CLINIC

Intravenous treatment (ambulatory)

- possibility of continuing work / school
- increased patient comfort & convenience
- hospitalization costs avoided
- freeing-up of hospital beds
- avoid risk of hospital acquired cross-infection
- ⇔ too sick patients need hospitalization

Intravenous treatment (ambulatory-continuous)

- most experience with ceftazidime-monotherapy
- concerns:
  - stability at room °t (prolonged exposure in continuous treatment)
  - stability at 37°C less studied (↑ °t under clothes, warm weather, …)
  - refrigeration may alter elastomeric characteristics (must be taken out 2h before administration)
  - solvens (no glucose – diabetes)

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Intravenous treatment (ambulatory-continuous)

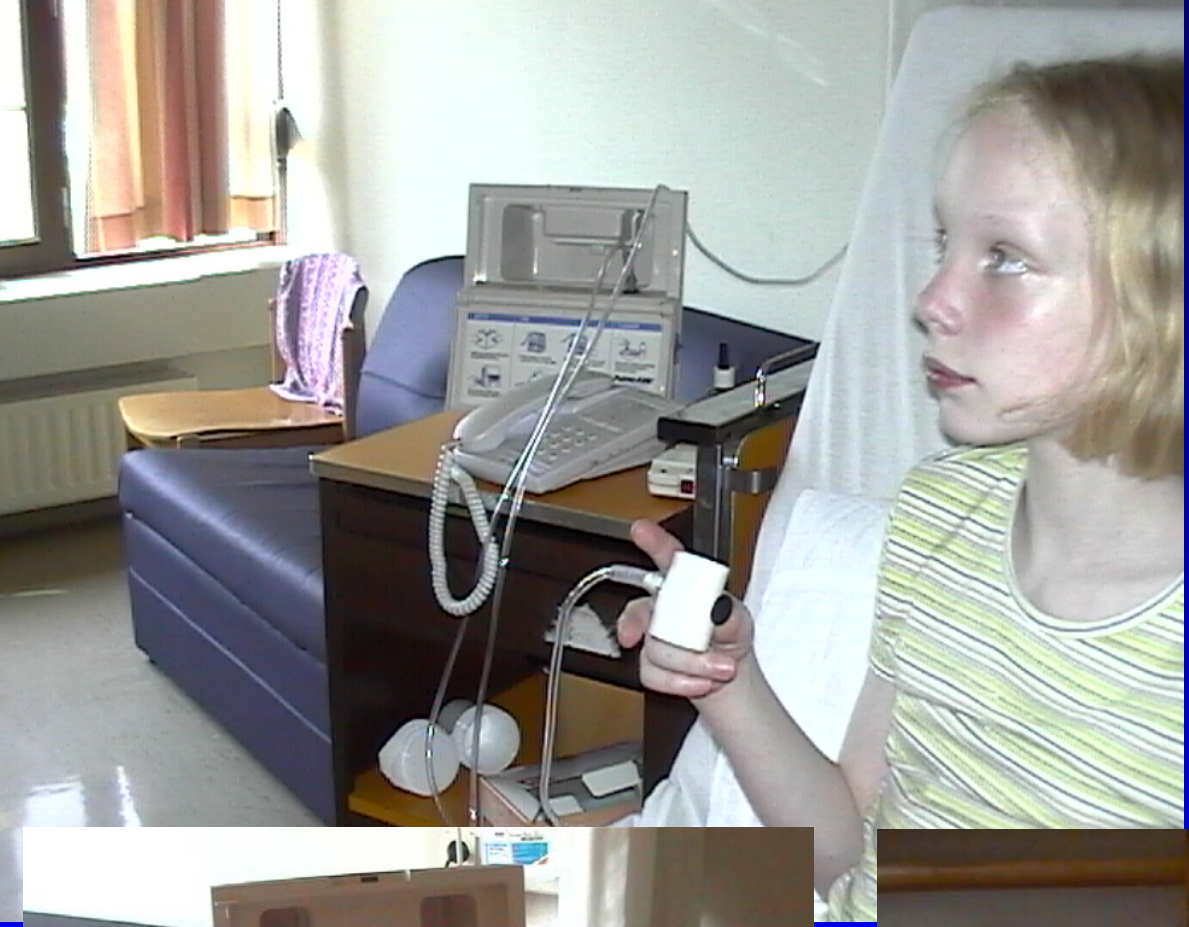
- Stability studies:
  - Ceftazidime (Tulkens. JAC 2003, Antimicrob.Agents Chemother.2002,-2001,Vinks. JAC 1997)
  - Several anti-*Pa* β-Lactams (Tulkens.Antimicrob.Agents Chemother.2002,Vinks. Rev Med Microbiol 1999)

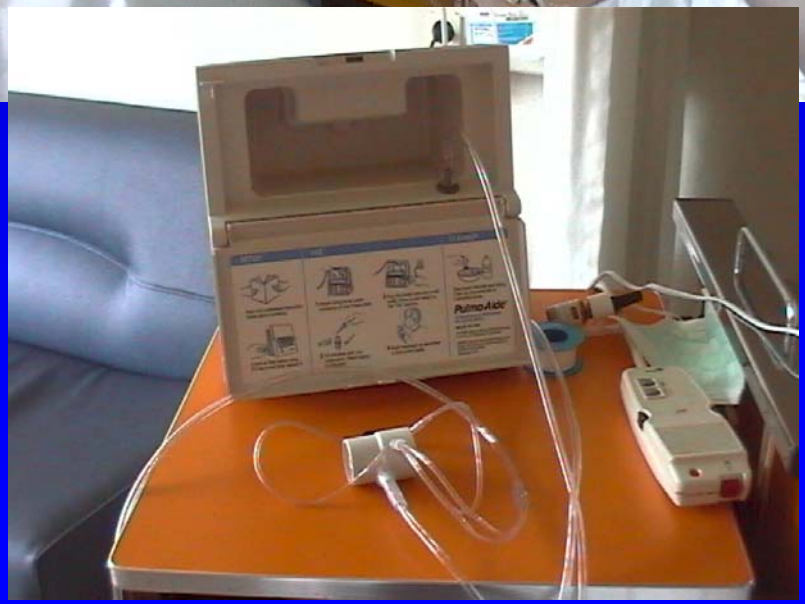
- ***Conclusions: ceftazidim, aztreonam, pip/taz most stable***

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Nebulized antibiotic therapy





ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Nebulized treatment (ambulatory)

- at 1st isolation of *Pa*
- long-term
  - Tobramycin: 5-10 mg/kg
  - Amikacin: 15-30 mg/kg

  } doses not well established
  - Colimycin: 10^6 to 2. 10^6 U/aerosol 2 or 3x/day
  - TOBI® 300mg/ aerosol 2x/d -- 28d ON/28d OFF
    - > 6y, not licensed for eradication in young CF
- combination with 3 weeks oral courses (Cipro)
- stopped when IV administration

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Nebulized treatment (ambulatory)

Many studies

aminoglycosides & colimycin

reduction in pulm exacerbation

no emergence of resisitance

no systemic toxicity (babies? high doses? long-term?)

Future: dry powder delivery devices

Local sides effects:

bronchoconstriction (hypertonic sol)

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

Antibiotic strategies against *Pa*: future studies

- AB dosages (IV-neb)
- Daily treatment ⇔ alternate monthly (neb)
- Neb mono ⇔ neb + oral courses
- IV mono ⇔ IV + neb high doses (exacerbation)
- Course frequency in chronic infection
- Treatment on demand ⇔ regular treatment (4x/y ???)
- Chronic oral azithromycin association
- Early intervention:
  - Before *Pa* isolation???
  - At 1st isolation => duration after eradication

    - Döring. ERJ 2000

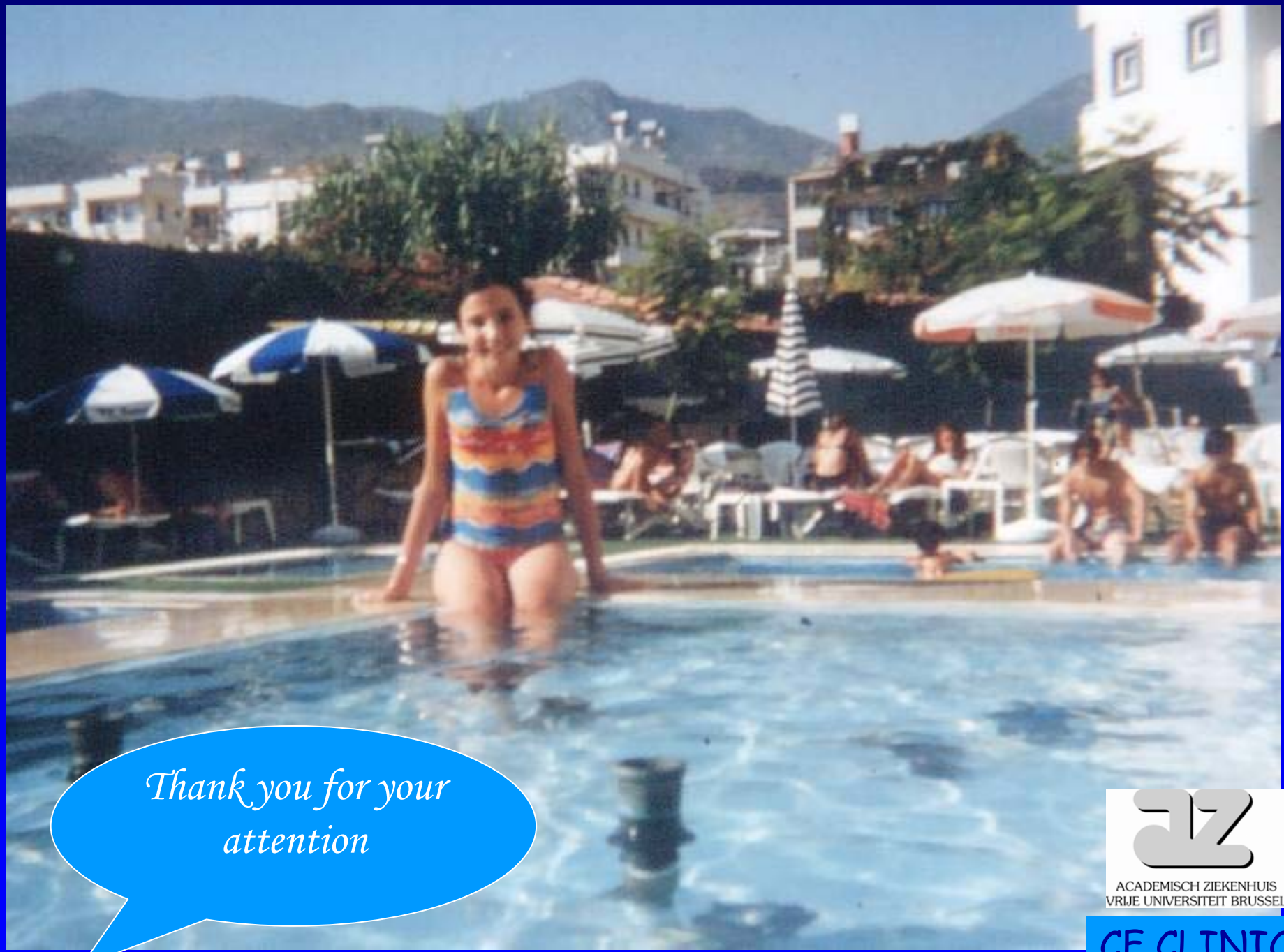
NOT ONLY AB ARE NEEDED IN CF

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC

ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC



ACADEMISCH ZIEKENHUIS
VRIJE UNIVERSITEIT BRUSSEL

CF CLINIC