P. aeruginosa: Present therapeutic options in Intensive Care

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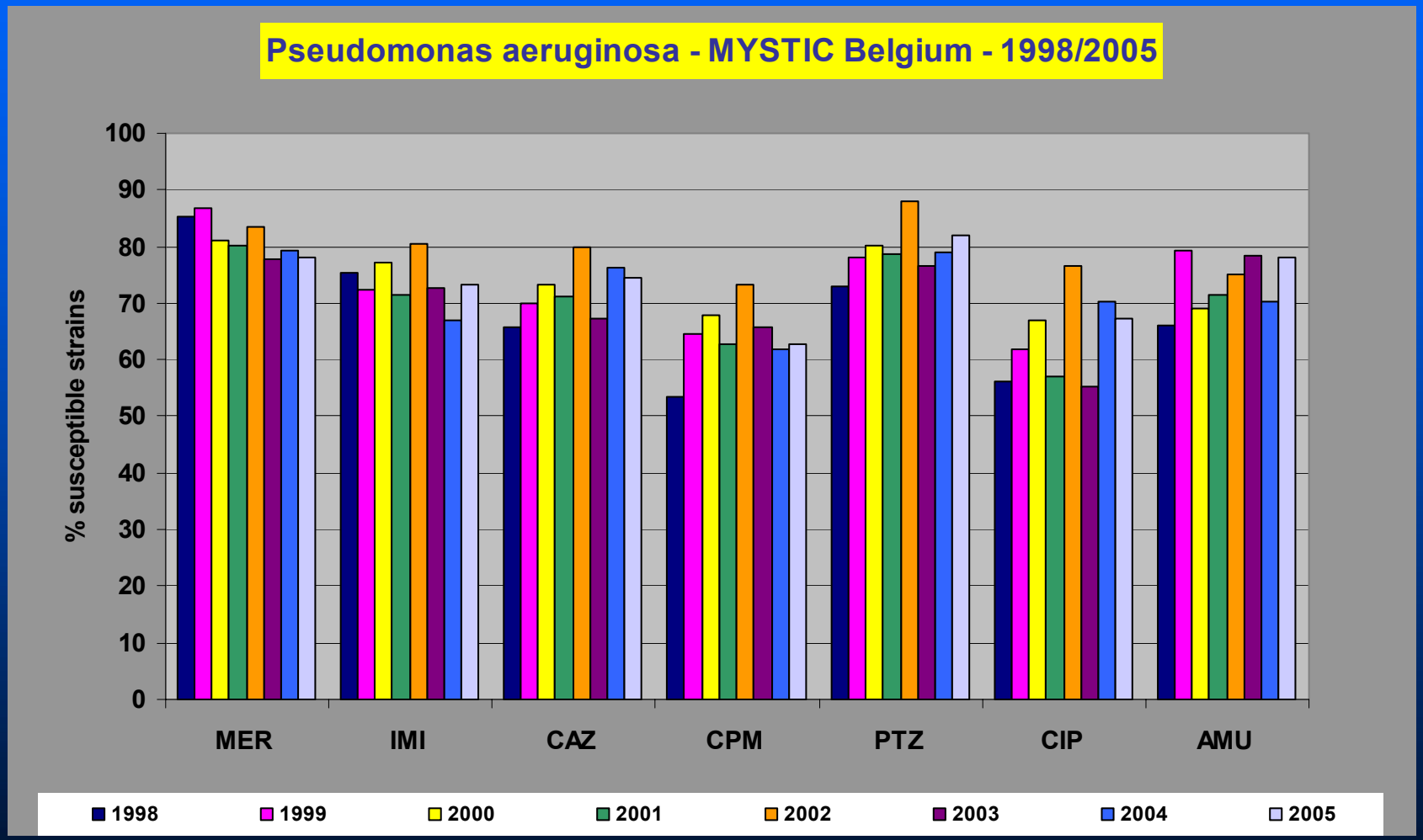
TABLE 201.1. Infections Caused by *Pseudomonas aeruginosa*

- Acquired immunodeficiency syndrome–related infections
- Bacteremia
  - Primary
  - Secondary
- Bone and joint infections
  - Sternoarticular pyarthrosis
  - Vertebral osteomyelitis
  - Symphysis pubis infection
  - Osteochondritis of the foot
  - Chronic contiguous osteomyelitis
- Central nervous system infections
  - Meningitis
  - Brain abscess
- Ear infections
  - Otitis externa
  - Malignant external otitis
  - Chronic suppurative otitis media
- Endocarditis
  - Native heart valve infection in intravenous drug users
  - Prosthetic heart valve infection
- Eye infections
  - Keratitis (corneal ulcer)
  - Endophthalmitis
- Gastrointestinal infections
  - Necrotizing enterocolitis
  - Shanghai fever
- Respiratory infections
  - Pneumonia
    - Nonbacteremic
    - Bacteremic
  - Lower respiratory tract infection in cystic fibrosis
- Skin and soft tissue infections
  - Ecthyma gangrenosum
  - Pyoderma
  - Wound infection
  - Dermatitis
  - Burn wound sepsis
- Urinary tract infections
  - Acute
  - Chronic (frequently with sites of persistence or obstruction)

Activity vs *Pseudomonas aeruginosa*



n=263 n=211 n=233 n=264 n=214 n=204 n=242 n=260

Susceptibility Patterns for Pseudomonas aeruginosa : Total vs non-CF strains

	2002			2003		
	Total		Non-CF	Total		Non-CF
	(n=175)		(n=140)	(n=237)	P value	(n=184)
MEM	88.6		87.1	76.8	0.02	82.1
IPM	78.9		77.9	71.7	NS	77.2
CAZ	78.3		78.6	67.5	0.02	76.6
CPM	74.3		75.0	58.1	0.001	67.8
P+T	86.9		86.4	77.2	0.01	78.8
CIP	76.6		79.3	57.0	<0.001	68.5
AMK	80.0		87.9	68.2	0.01	76.0

⇒ Increase in resistance: affected by CF isolates !

Multi Drug Resistant Isolates of *Pseudomonas aeruginosa* 1997 - 2004

Country	N° Centers	N° of isolates (%)	
		Ps.aeruginosa	MDR
Belgium	8	1613	152 (9.4)
Czech Republic	1	164	39 (2.4)
Germany	7	1799	172 (9.6)
Italy	3	1111	252 (22.7)
Poland	1	178	3 (1.7)
Russia	1	160	41 (25.6)
Sweden	4	267	5 (1.9)
Turkey	9	1280	383 (29.9)
UK	5	1056	82 (7.8)

MONOTHERAPY

COMBINATION THERAPY

Sepsis(1)

- ***Mica Paul et al BMJ 2004***
- Meta-analysis of 64 randomized trials
  with 7586 non neutropenic patients
  → betalactam = betalactam + aminoside
  on the basis of all cause fatality
  - No advantage among patients with
    P. aeruginosa infection (426 patients)

Sepsis(2)

- Clinical failure more common with combination treatment
- No difference in the rate of development of resistance

  $\Rightarrow$ lack of compelling data to support the initial use of combination therapy…

Combination versus monotherapy

Bodey et al Arch Int Med 1985

- Retrospective study in 410 cancer patients with P. aeruginosa septicemia of MD Anderson Cancer Center
- 1/3 with pneumonia

  $\rightarrow$ betalactam monotherapy = combination

  $72 \leftrightarrow 71\%$
- NB : very poor outcome if monotherapy with an aminoglycoside (29%)

Combination versus monotherapy

- ***Hilf,Yu et al Am J Med 1989***
- 200 patients with P. aeruginosa septicemia

  Prospective study
- Mortality : 27% (combination) ↔ 47% (mono)
- BUT : less potent AB than now
- < 10% had received pipera, cefta or imipenem
- Alternative conclusion :
  combination therapy is superior to an amino alone!

Combination versus monotherapy in P.aeruginosa septicemia

- Since 1989 : several studies :
  - ☑ same outcome
  - Vidal Arch Int Med 1996(189 pat)
  - Kuikka Eur J Clin Microb Infect Dis 1998
  - Sigman Int J Inf Dis 1998 (123 pat)
  - Chatzinikolaou Arch Int Med 2000(145 pat)
  - Chamot AAC 2003
  - BUT : majority of ID experts still favor use of a combination, especially if S to the betalactam agent is ≤80%

Endovascular infections

- Rare cases of endocarditis (esp.drug addicts)
- Case reports of failure with several mono/combination therapy
- Meropenem and tobra sucessfull in one case
- Association of rifampin with carbenicillin / amino effective in 2 cases clinically R to the combination.(Yu AAC 1984)

Nosocomial pneumonia (1)

- P. aeruginosa in the three leading pathogens in most VAP studies
  - High failure rate with aminoglycosides alone (historic data)
  - No data for inclusion of amino for fully S organisms(not optimally active in the lungs at concentration obtained with IV administration)
- No prospective study of a betalactam with or without a FQ

Nosocomial pneumonia (2)

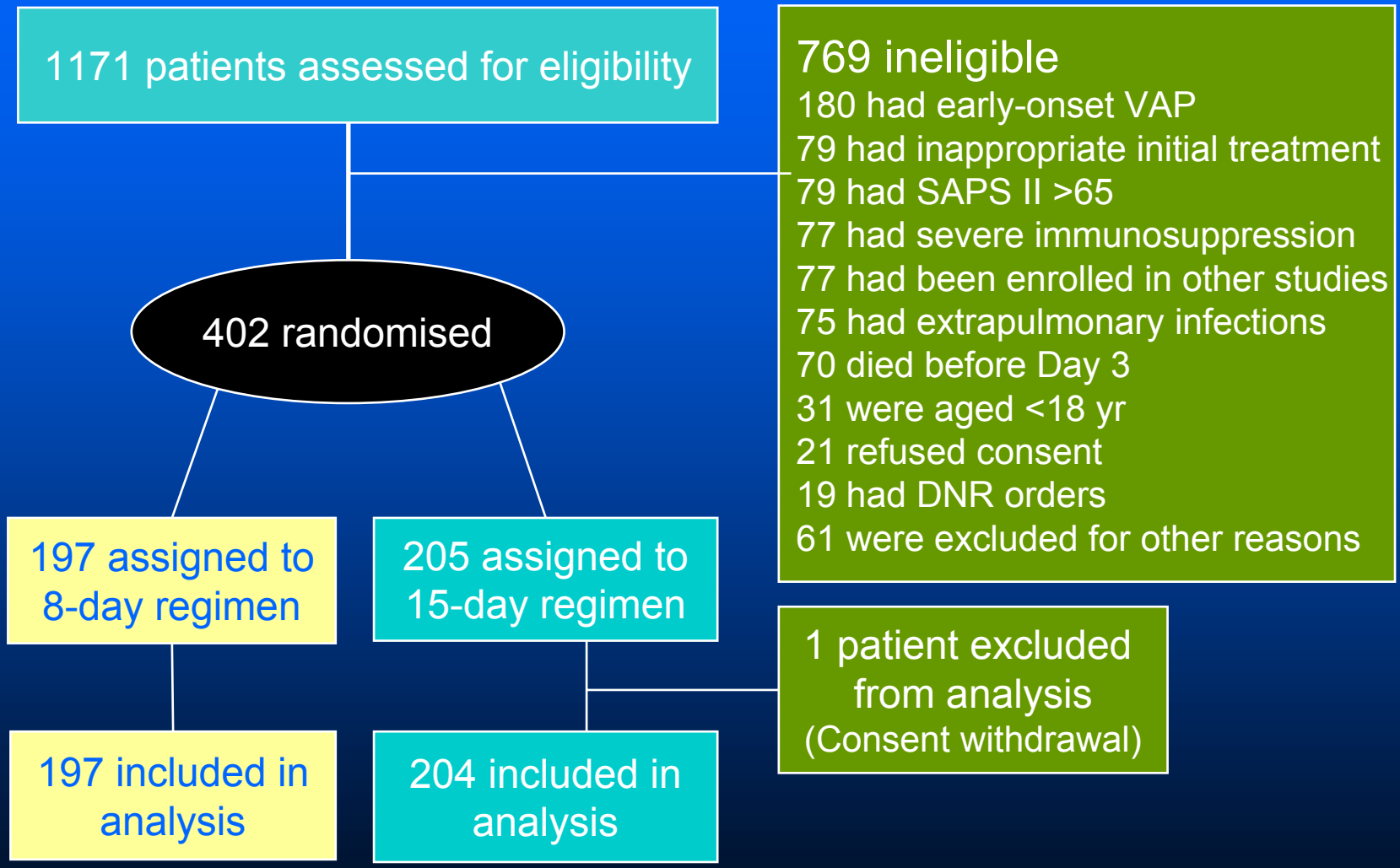
- No data for aerosolized administration in ACUTE P. aeruginosa pneumonia :
  - Small DBR study in VAP due to various pathogens (Brown AAC 1990) but potential efficacy in MDR P.aeruginosa pneumonia (case reports)
- No data showing prevention of development of R to imipenem by the addition of an aminoglycoside

(Cometta AAC 1994)

Comparison of 8 versus 15 days of AB therapy for VAP in adults

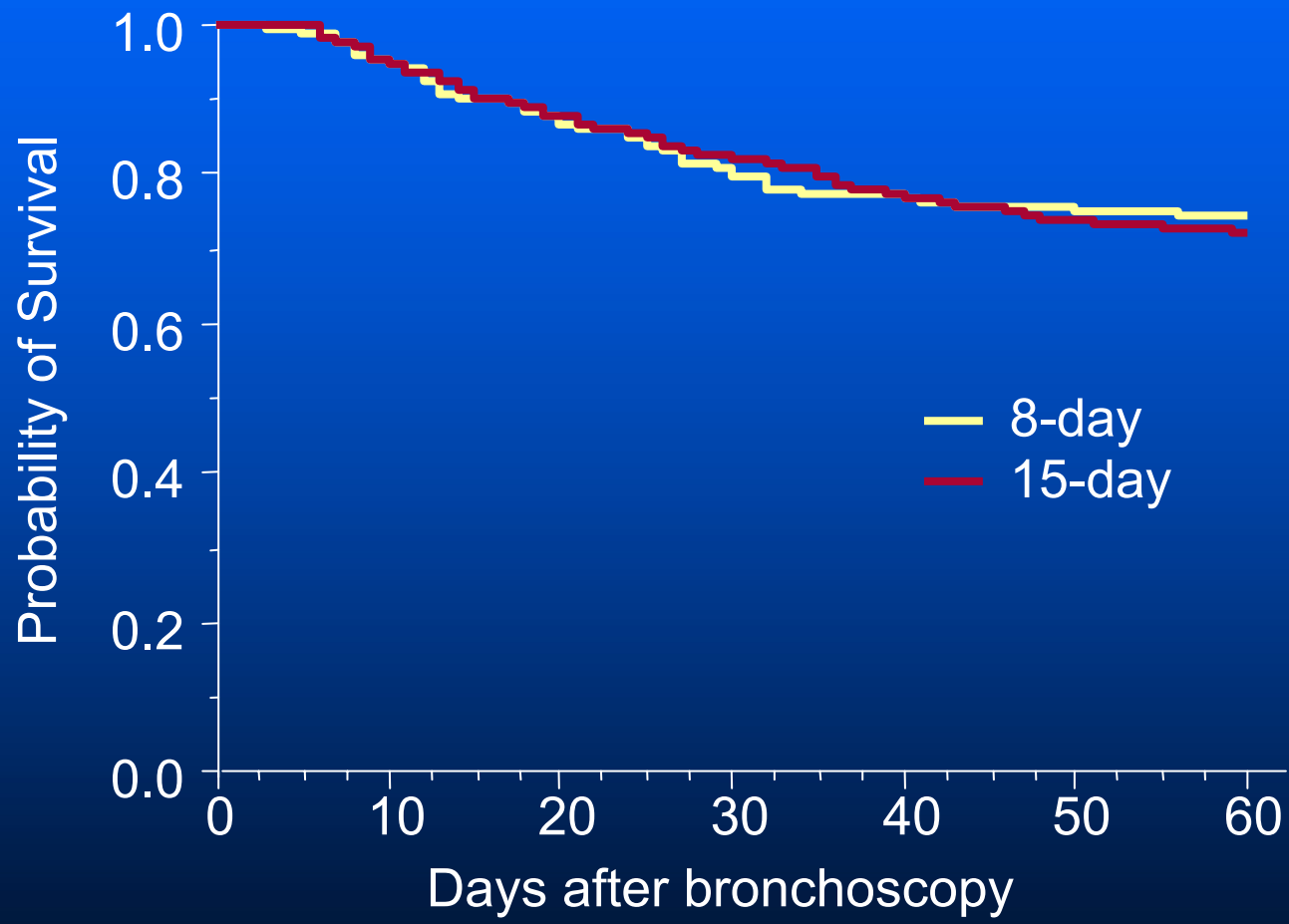
- ***Chastre et al***, *JAMA 2003*
- Prospective, randomized, double-blind study
  (until day 8)
- 51 ICU in France - From 6/99 to 6/02
- Either short course of AB : 8 days
  long (classic) course : 15 days
  with BAL at D1

Study Design



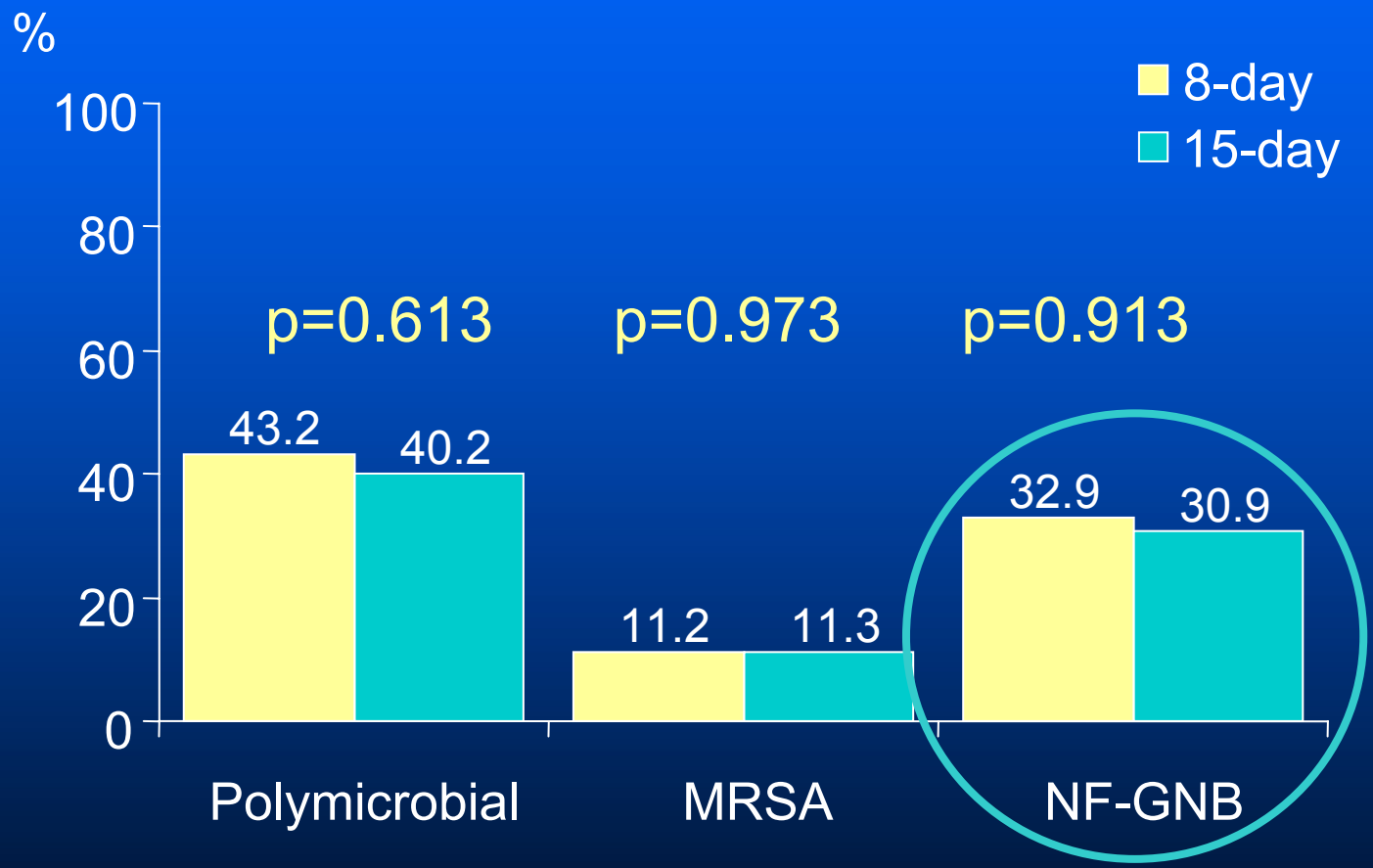
Chastre, Wolff, Fagon, et al. JAMA 2003

Cumulative Survival Estimates According to Duration of Antimicrobial Treatment



Chastre, Wolff, Fagon, et al. JAMA 2003

Bacteriology



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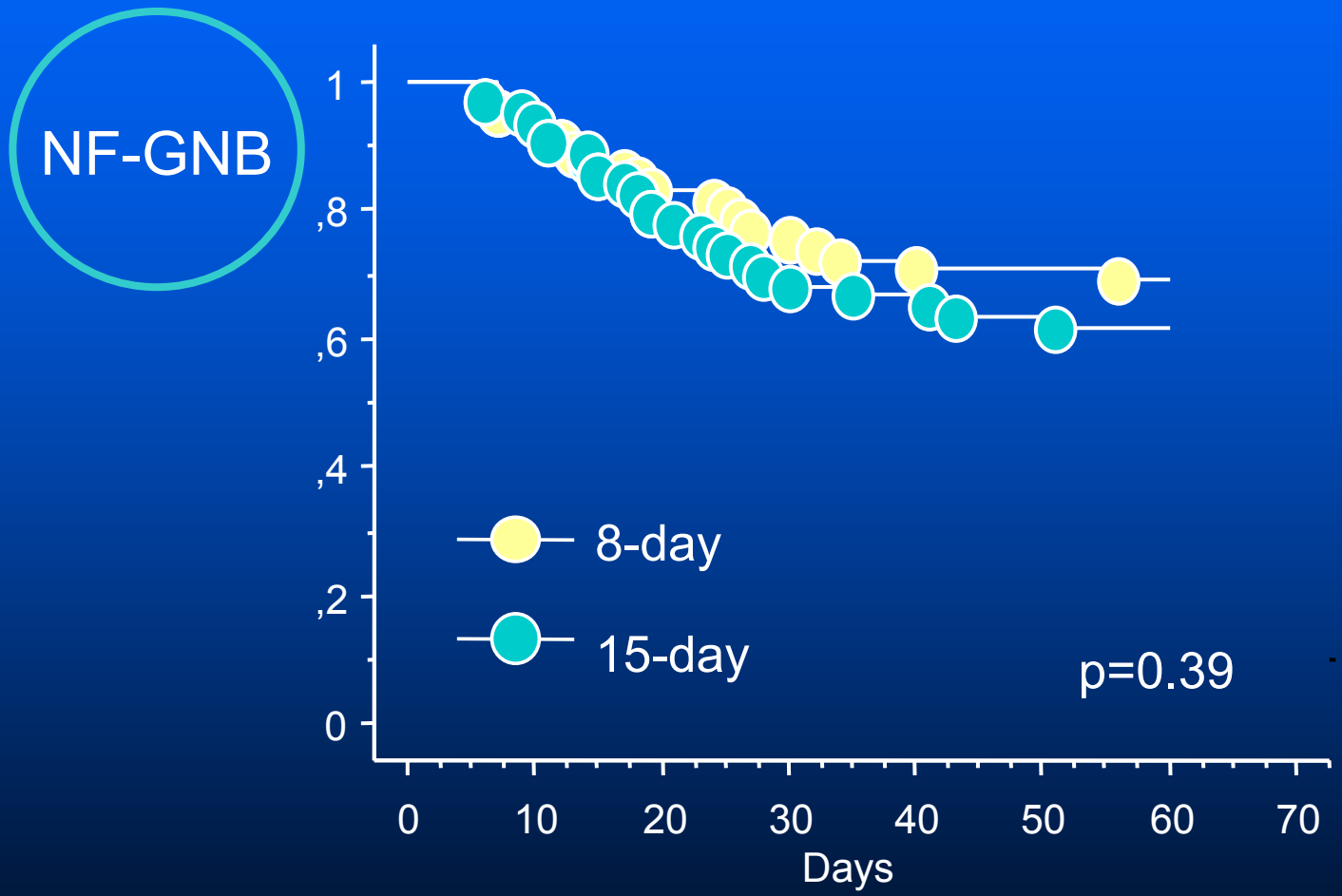
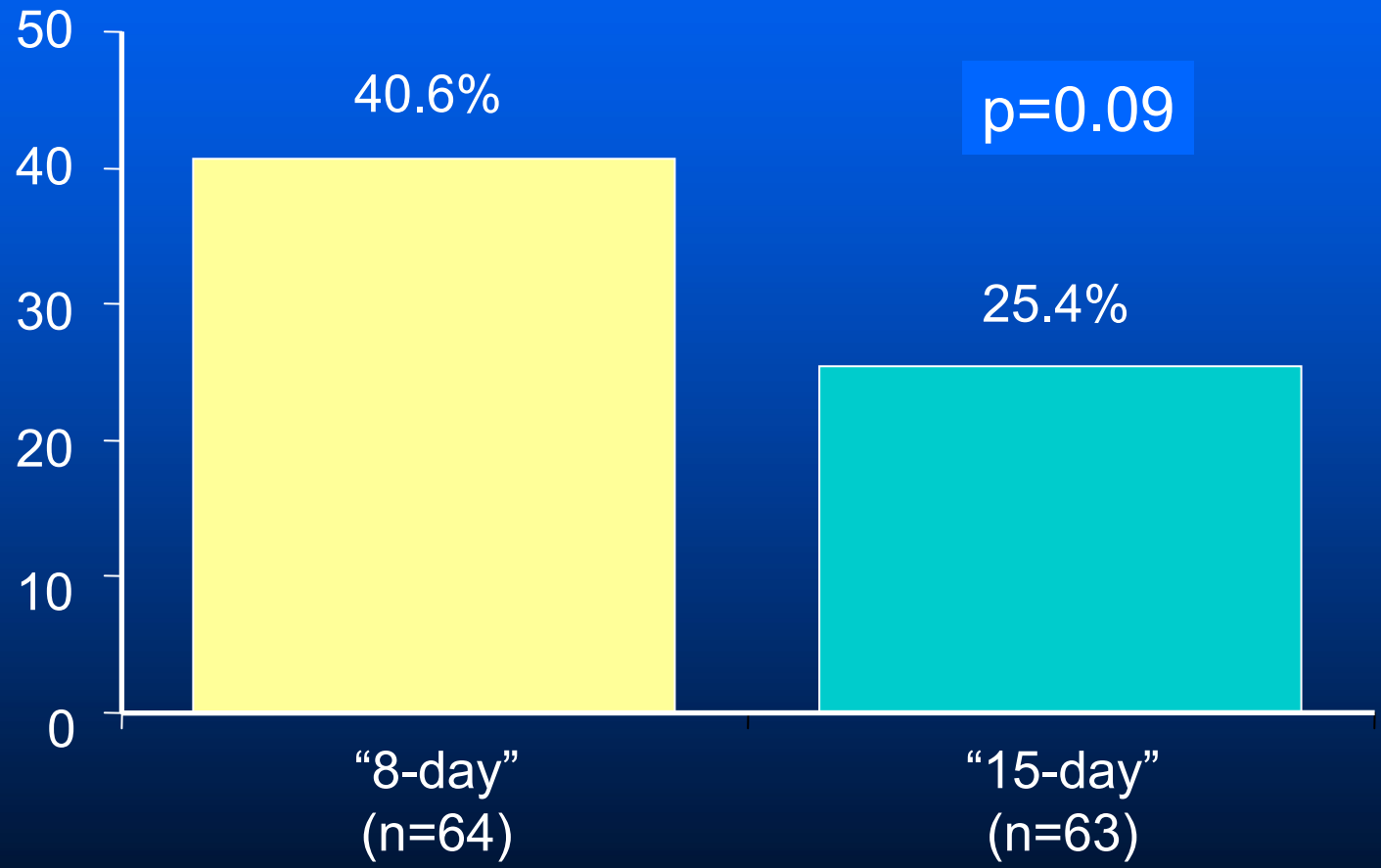


Chastre, Wolff, Fagon, et al. JAMA 2003

Percentages of Pulmonary Infection Recurrence According to Antimicrobial Therapy Duration (NF-GNB)



Chastre, Wolff, Fagon, et al. JAMA 2003

Febrile neutropenia (1)

- Historically : leading pathogen

  → less common (prophylaxis,…)
- IDSA Guidelines :

  - ceftazidime or cefepime or carbapenem

    +/- aminoglycoside

  - antipseudomonal penicillin + aminoglycoside also valid option

Febrile neutropenia (2)

- ***Mica Paul et al BMJ 2003***

  Meta- analysis of 47 randomized trials/7807 p

  → no significant difference in all cause fatality

  - significant advantage with monotherapy for success
  - similar rate of superinfection
  - more adverse events in the combination treatment group (not reduced by OD amino dosing)

MENINGITIS(1)

- Secondary to a neurosurgical procedure, head trauma or bacteremia
- Few published experience:
  - ceftazidime has the « largest »published data
    - » Fong Rev Inf Dis 1985
    - » Marove Chemotherapia 1985
    - » Norrby Am J Med 1985

MENINGITIS (2)

- Less data with : cefepime

  meropenem (*Chmelik JAC 1993*)

- Data in Gram (-)meningitis

  with aztreonam (not specifically with P. aeruginosa)

  Kilpatrick Scand J Inf Dis 1981

  with ciprofloxacin

  Wong CID 1997

MENINGITIS(3)

- Unproved necessity of an aminoglycoside, unless betalactam R organism (then by intrathecal administration)
- Length of therapy : empiric!
  ≥ 2 weeks(with removal of any foreign bodies)

UTI

- (Nearly)by definition a «complicated UTI»
  stone, stent, catheter, instrumentation,…
- No comparative data on specific therapies :
  - antipseudomonal betalactams
  - aminoglycosides
  - fluoroquinolones(esp. ciprofloxacin)
- Duration : 7-14 days (acute pyelon.)

cSSTI

- Burn wounds,…

  → Extensive debridement
- Ceftazidime(or cefepime, or aminopen or carbapenem)
- NB : rapid development of R in one study with imipenem monotherapy….

Mode of administration

- Continuous infusion of a betalactam :

  no clinical study on P. aeruginosa infection

- OD or multiple doses of an aminoglycoside :
  - No prospective data showing a better outcome

Conclusion

- Knowledge of LOCAL epidemiology
- Monotherapy with a potentially active betalactam at « high doses »

  +/- initial association in severe infections with :

  - an aminoglycoside IF low local R levels

    non pulm. infect ?

  - a FQ IF low local R levels/pulm infect.

In units where R to betalactam ≥ 15-20%