Optimal Duration of Antibiotic Therapy

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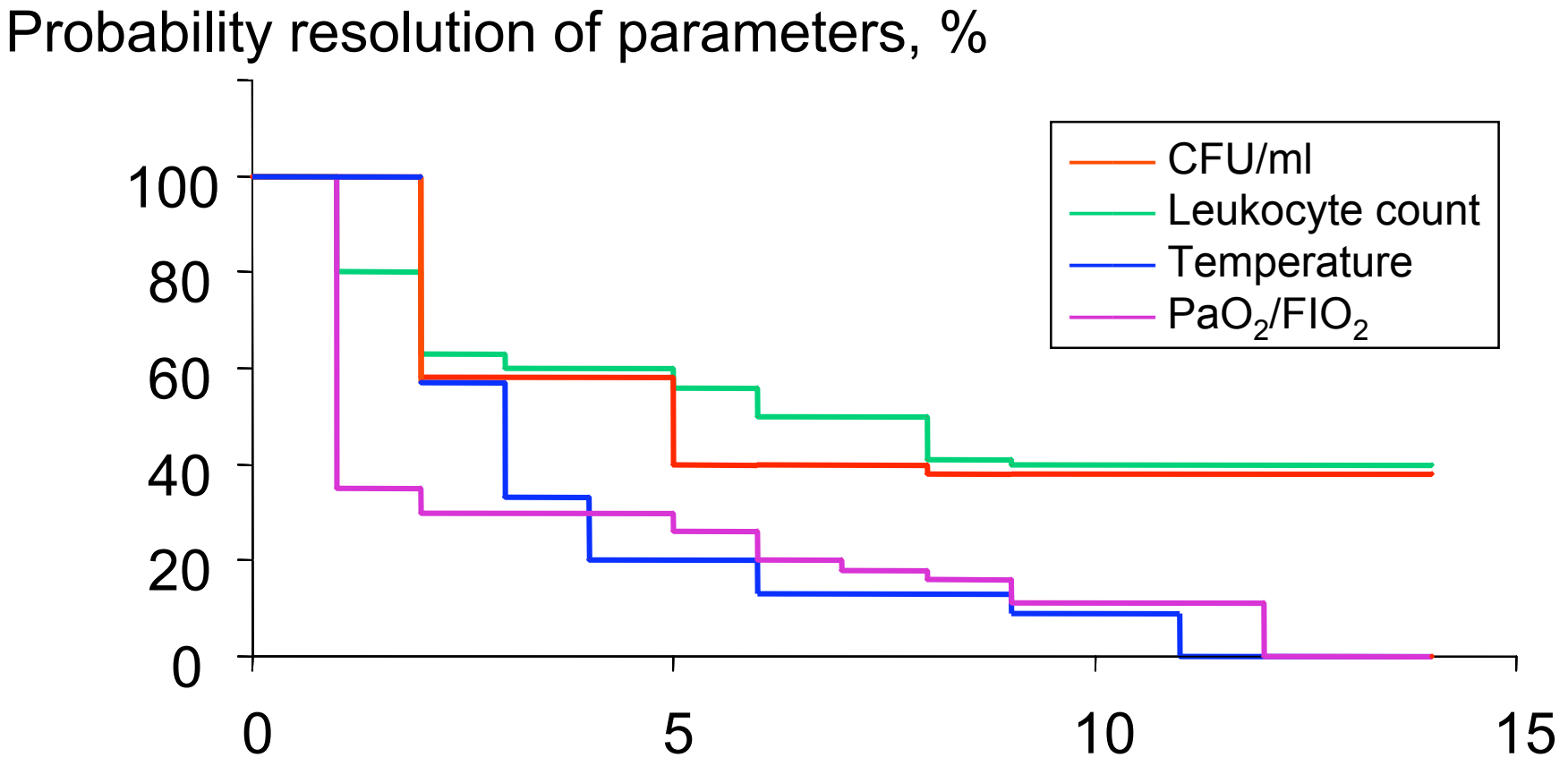
American Thoracic Society Guidelines for Therapy of VAP

Campbell, Niederman et al. Am J Respir Crit Care Med 1996

- Duration of therapy should be individualized, depending on the severity of illness, rapidity of clinical response, and infecting pathogen.
- Antibiotics should be continued for ≥ 14 days for pts with multilobar involvement, cavitation, or a necrotizing GNB pneumonia, and when infection is caused by *P. aeruginosa* or *Acinetobacter* spp.
- By contrast, for infection caused by MSSA or *H. influenzae*, a 7-10 d course of therapy may be adequate.

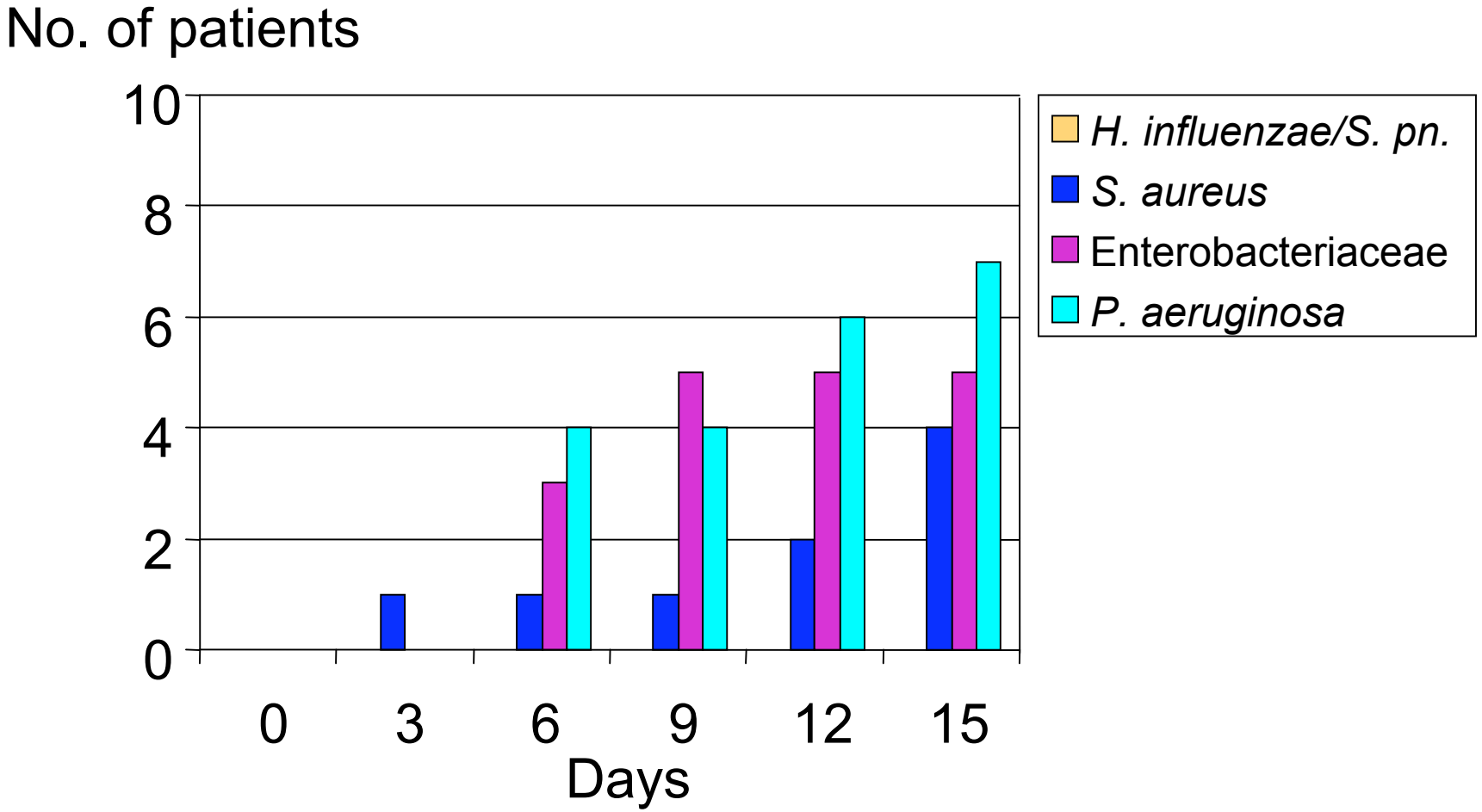
Probability of Resolution of Infectious Parameters after Antimicrobial Therapy in 27 Patients with VAP

Dennesen et al. AJRCCM 2001



Number of Patients with Newly Isolated Microorganisms from Endotracheal Aspirates after Initiation of Antimicrobial Therapy

Dennesen et al. AJRCCM 2001

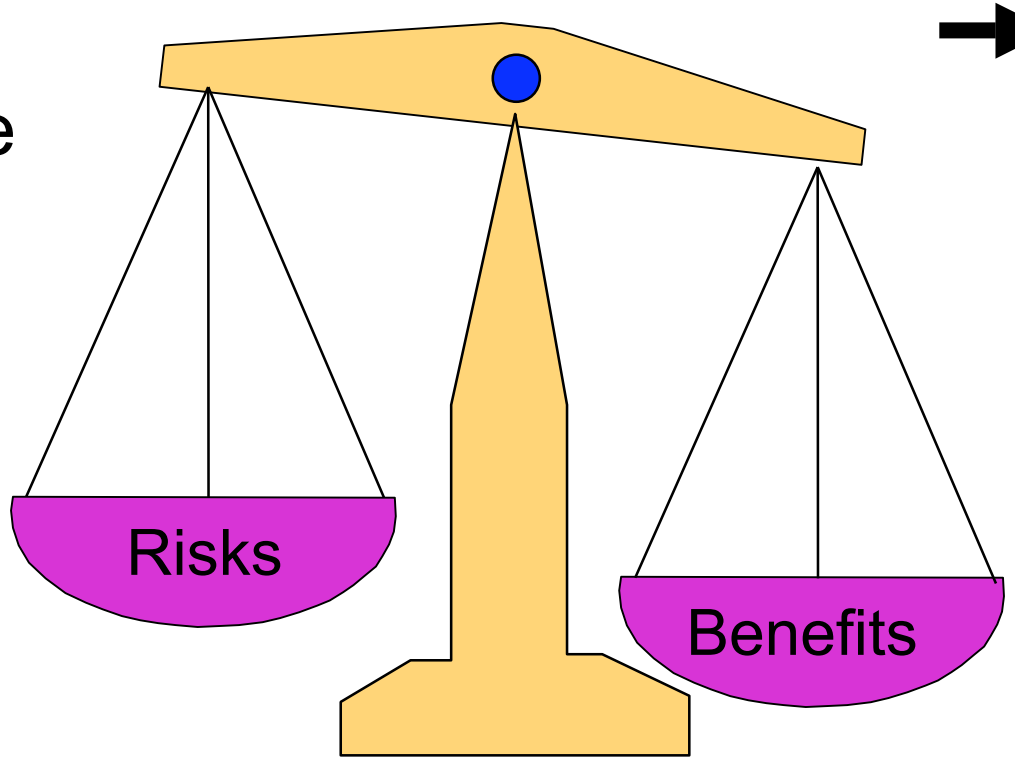


Factors Associated at Day 8 with Recurrence in 103 Patients with VAP

VARIABLE	CE(95% CI)P	Primary respiratc

Optimal Duration of Therapy for VAP: One Week vs Two Weeks

Failure
Relapse



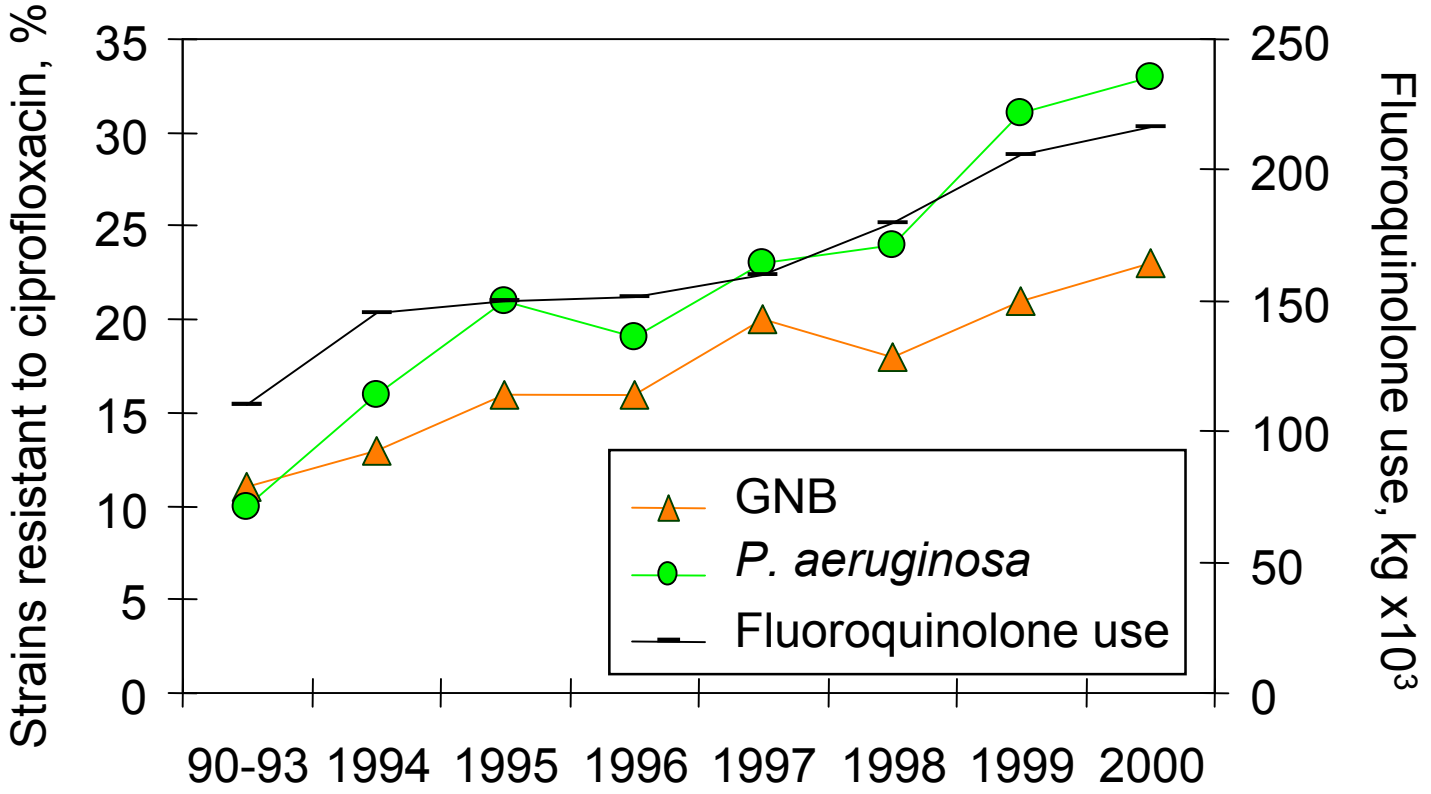
→ Control of antimicrobial resistance

Reduction of side effects

Reduction of costs

Fluoroquinolone Use and Resistance Rates in *P. aeruginosa* and Gram-negative Bacilli

Neuhauser et al. JAMA 2003;289:885-8



PneumA: A Comparison of Two Durations of Antibiotic Therapy for Treatment of VAP

A. Alvarez (Créteil), P. Asfar (Angers), S. Aubas (Montpellier), JP. Bédos (Le Chesnay), F. Blot (Villejuif), J Bocquet (Nancy), F. Brivet (Clamart), R. Bronchard (Beaujon), M. Canonne (Elbeuf), Y. Castaing (Bordeaux), J. Chastre (Pitié-Salpétrière), E. Clémenti (La Roche/Yon), P. Corne (Montpellier), JM Coulaud (Montfermeil), JL Diehl (HEGP), Y Domart (Compiègne), JY Fagon (HEGP), F. Fieux (St Louis), B. Garo (Brest), C. Gervais (Nîmes), J. Gonzalès (Garches), R. Gauzit (Bondy), S. Guyomarch (St Etienne), A. Jaeger (Strasbourg), J Hayon (St Germain en Laye), D. Huchon (Hôtel Dieu), P. Jusserand (Rouen) C. Lamer (Institut Montsouris), MJ Laisné (Lariboisière), C. Legall (Clamart), H. Mal (Beaujon), K. Nourdine (Roanne), A. Novara (HEGP), G. Offentsadt (St Antoine) H. Outin (Poissy), JL Pallot (Montreuil), C. Paugam (Bichat-Claude Bernard), D. Perrin (Evry), E. Pigné (Colombes), PF Perrigault (Montpellier), M. Pinsart (Dieppe), A. Roch (Marseille), M. Slama (Amiens), JP. Sollet (Argenteuil), F. Stéphan (Créteil), F. Thaler (Suresnes), F. Thomas (Diaconesses), G. Trouillet (Pontoise), JL. Trouillet (Pitié-Salpêtrière), B. Veber, (Rouen), D. Villers (Nantes), D. Wermert (Bicêtre), M. Wolff (Bichat-Claude Bernard), F. Zéni (St Etienne)

Design and Setting:

- Prospective, randomized, double-blind (until day 8), parallel-group trial performed in 51 ICUs in France from June 1, 1999 to June 6, 2002.
- Patients were randomly assigned to receive either a short (8-day) course of antibiotics or a long (15-day) course, as soon as it was possible for the investigators to verify that the inclusion/exclusion criteria were fulfilled, the first day of the study being the day corresponding to the bronchoscopy.

Inclusion Criteria:

- All patients who were receiving MV for at least 48 hours fulfilling the following criteria:
  - age older than 18 years;
  - clinical suspicion of VAP, defined by a new and persistent infiltrate on chest radiography associated with at least one of the following: purulent tracheal secretions, fever ≥ 38.3°C, and leukocytosis > 10,000/mm^3;
  - positive quantitative cultures of distal pulmonary secretion samples, obtained using bronchoscopy and BAL (≥ 10^4 cfu/ml) or with a PSB (≥ 10^3 cfu/ml);
  - and instigation within the 24 hours following FOB of an appropriate antibiotic therapy directed against the microorganism(s) responsible for the pulmonary infection, as determined by their susceptibility patterns;

Primary Outcome Measures:

- Death from any cause.
- Microbiologically documented pulmonary infection recurrence, defined using the same microbiologic criteria as those that led to the inclusion of the patients in the trial.
- Antibiotic-free days,

All were assessed 28 days after the onset of pneumonia.

Follow-up:

- Extreme vigilance for pulmonary infection recurrence was maintained throughout the study period and fiberoptic bronchoscopy was performed as soon as:
  - a patient became febrile,
  - had purulent tracheal secretions,
  - and/or developed a new pulmonary infiltrate or when an existing infiltrate progressed.
- Distal pulmonary secretions were also collected:
  - in case of unexplained hemodynamic instability;
  - in case of unexplained deterioration of blood gases;
  - or when an intercurrent event imposed an urgent change of antibiotic therapy, regardless of the reason.

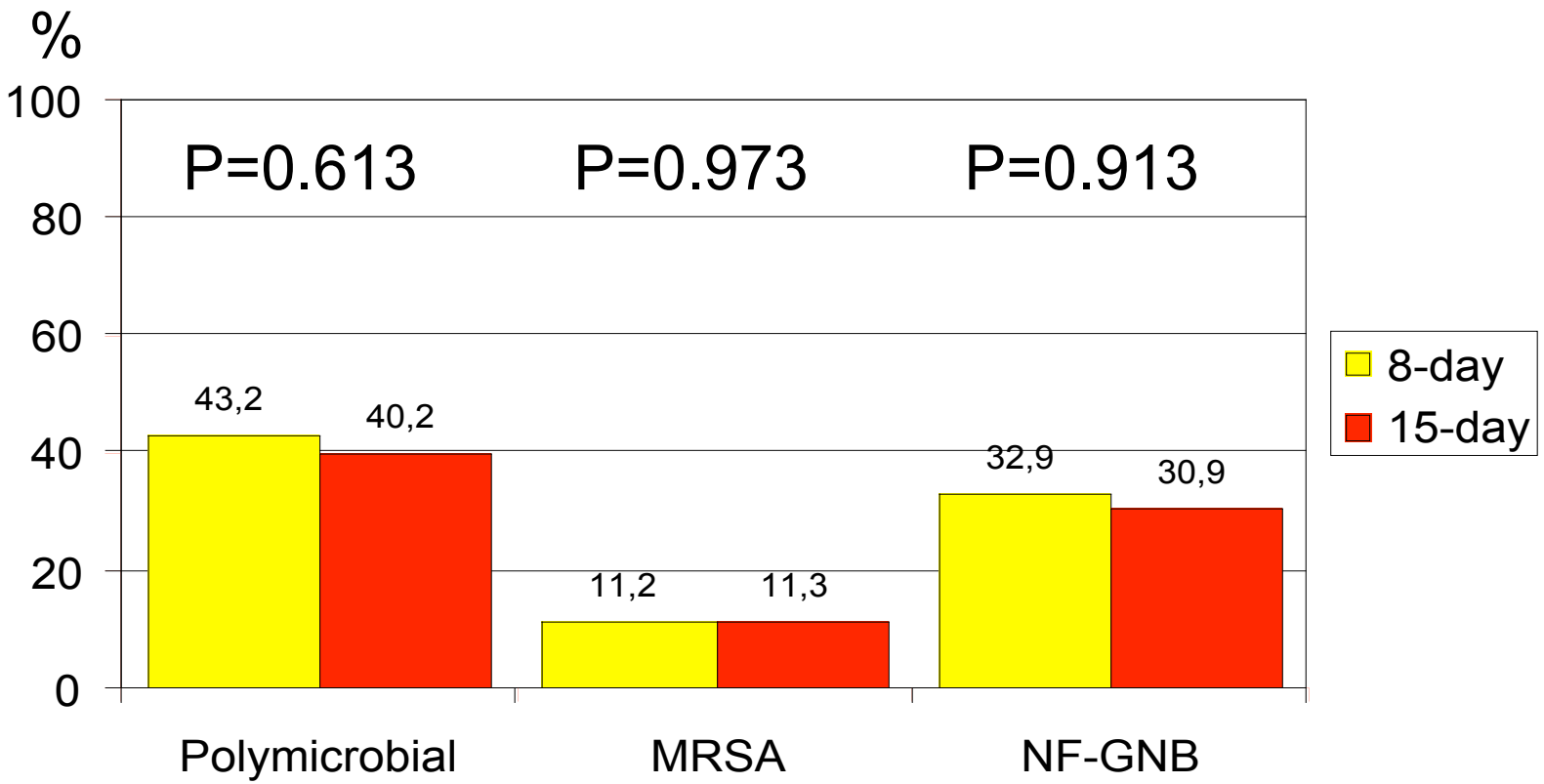
Baseline Characteristics:

MEDIAN (Q1-Q3)8-DAYN=19715-DAYN=204P-			Age, year63

Baseline Characteristics:

MEDIAN (Q1-Q3)8-DAYN=19715-DAYN=204P- Radiologic sc

Bacteriology:

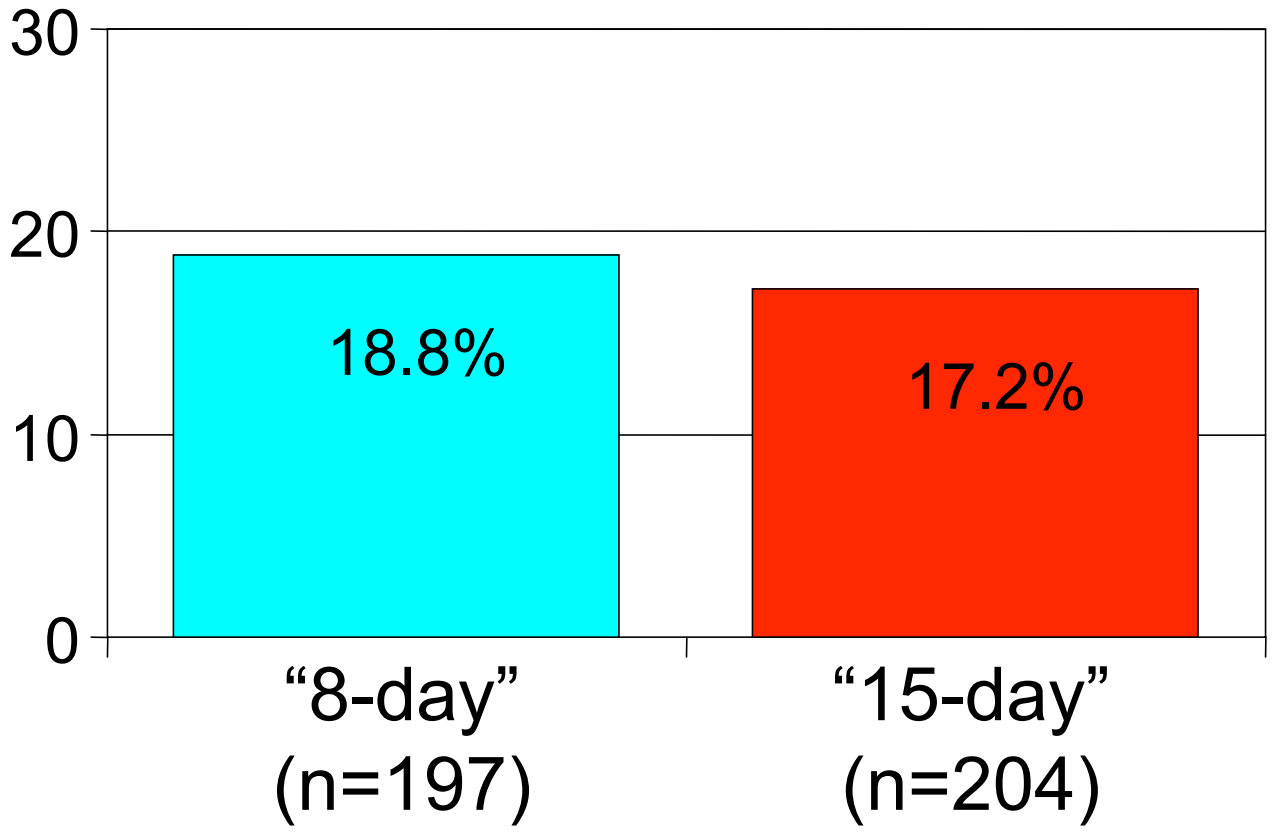


Results:

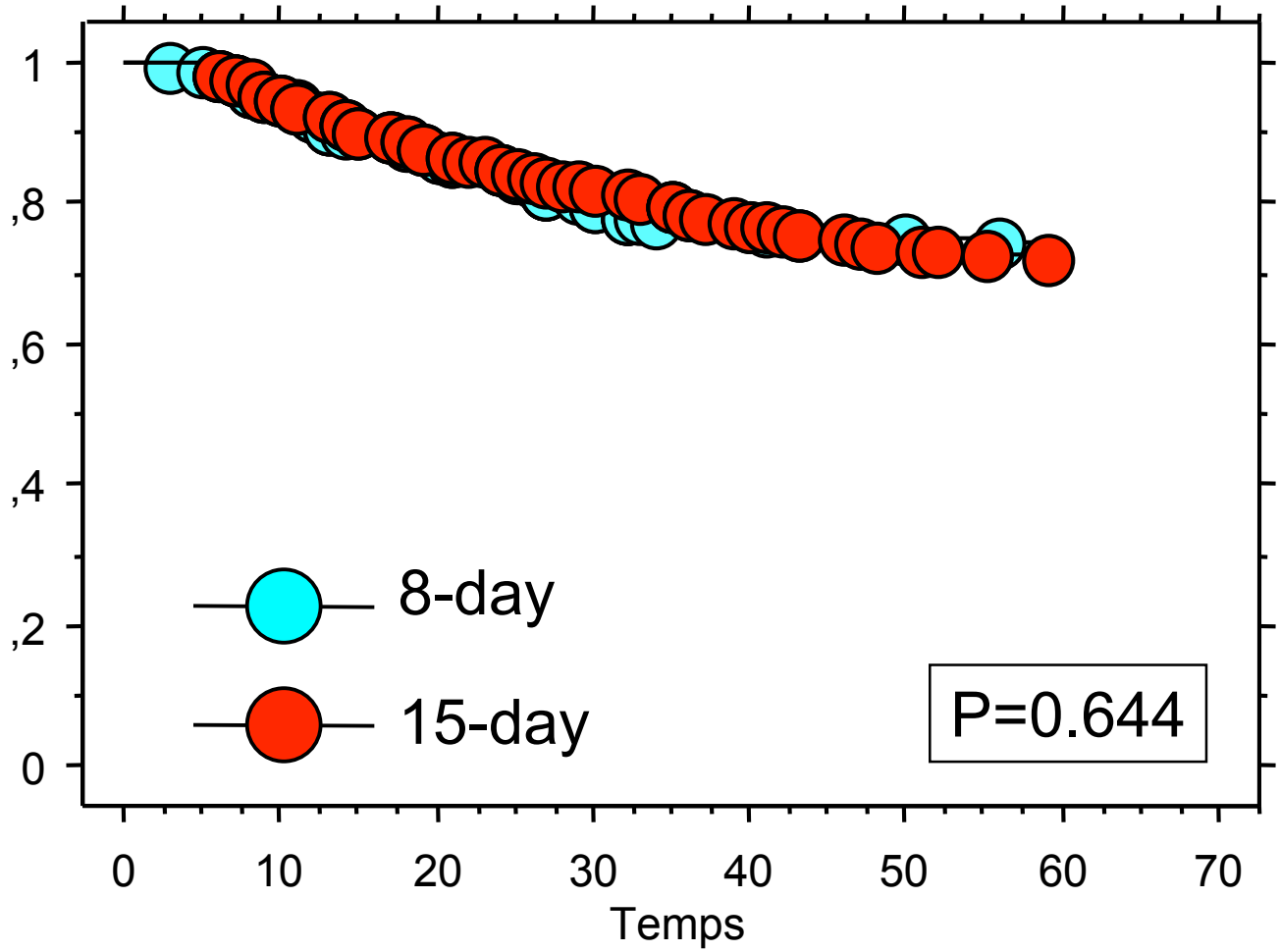
- Primary outcome measures

Mortality Observed at Day 28 According to Duration of Treatment

Difference, +1.6% [90% CI, -3.7 to +6.9%]

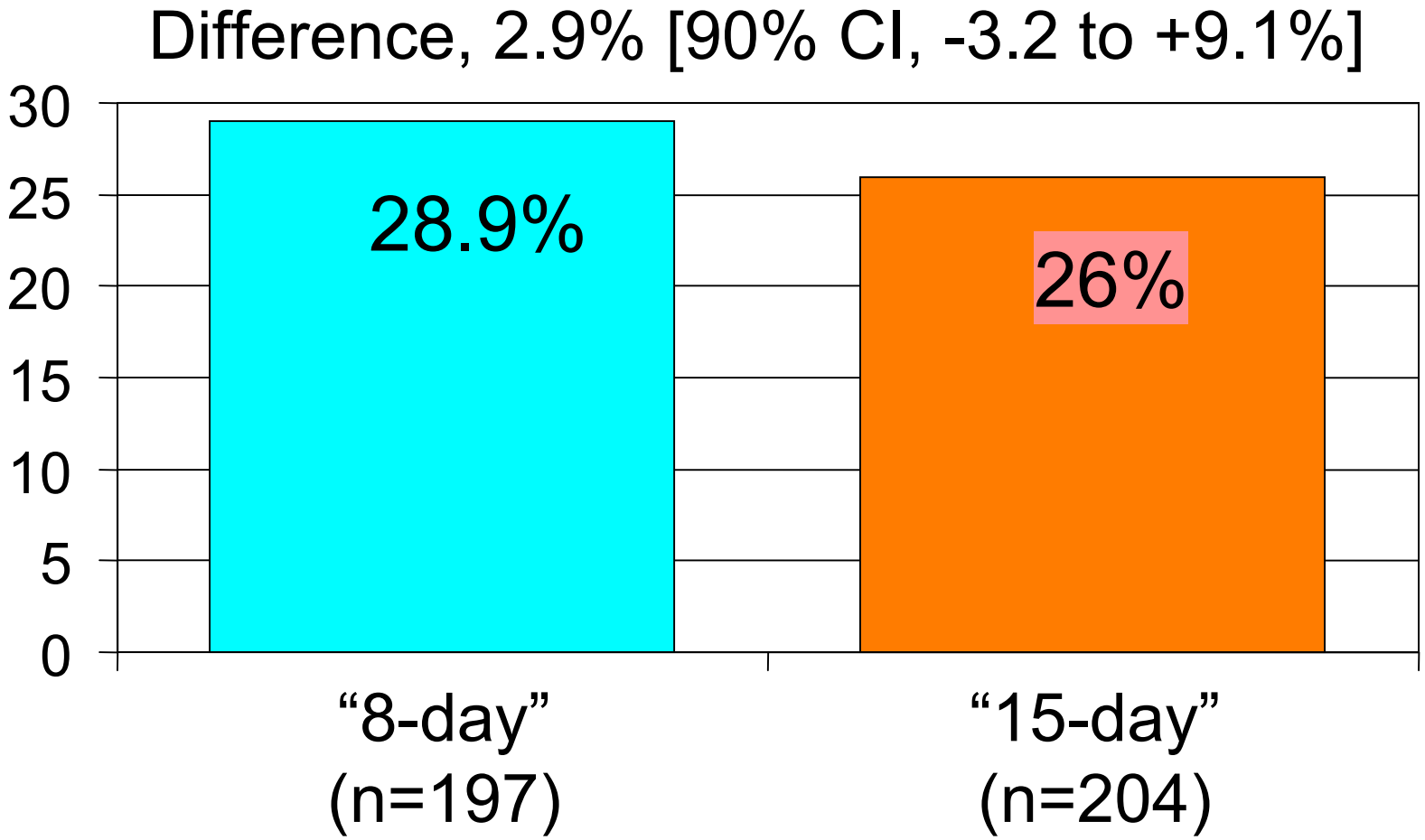


Cumulative 60-Day Survival Estimates Among 401 VAP Patients Assigned to Short (8 days) or Long (15 days) Duration of Antimicrobial Treatment



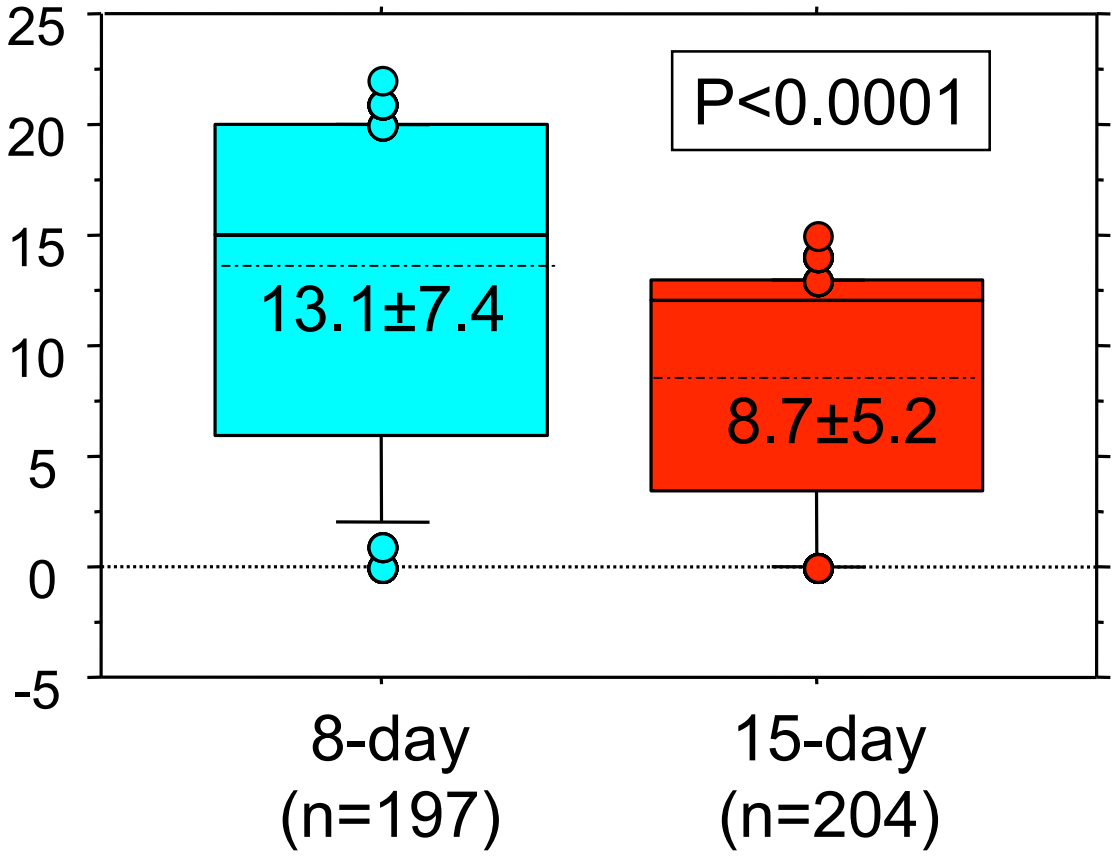
Percentages of Pulmonary Infection Recurrence According to Antimicrobial Therapy Duration

Chastre, Fagon, Wolff, for the PneumA Trial Group



Number of Days "Alive" Without Antibiotic Therapy According to Antimicrobial Therapy Duration

Mean difference, + 4.4 days (95% CI, 3.1 to 5.6 days)



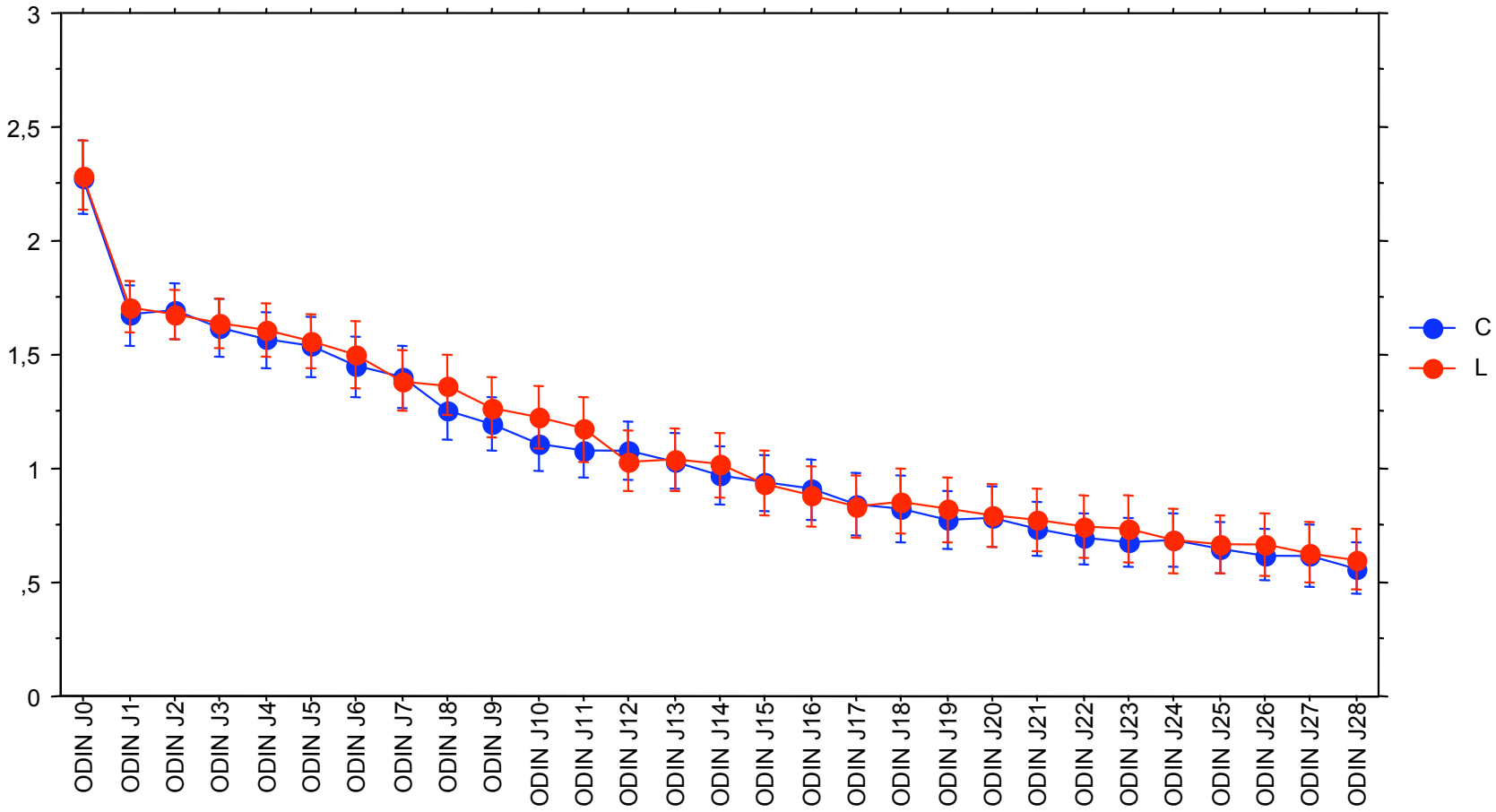
Results:

- Secondary outcome measures

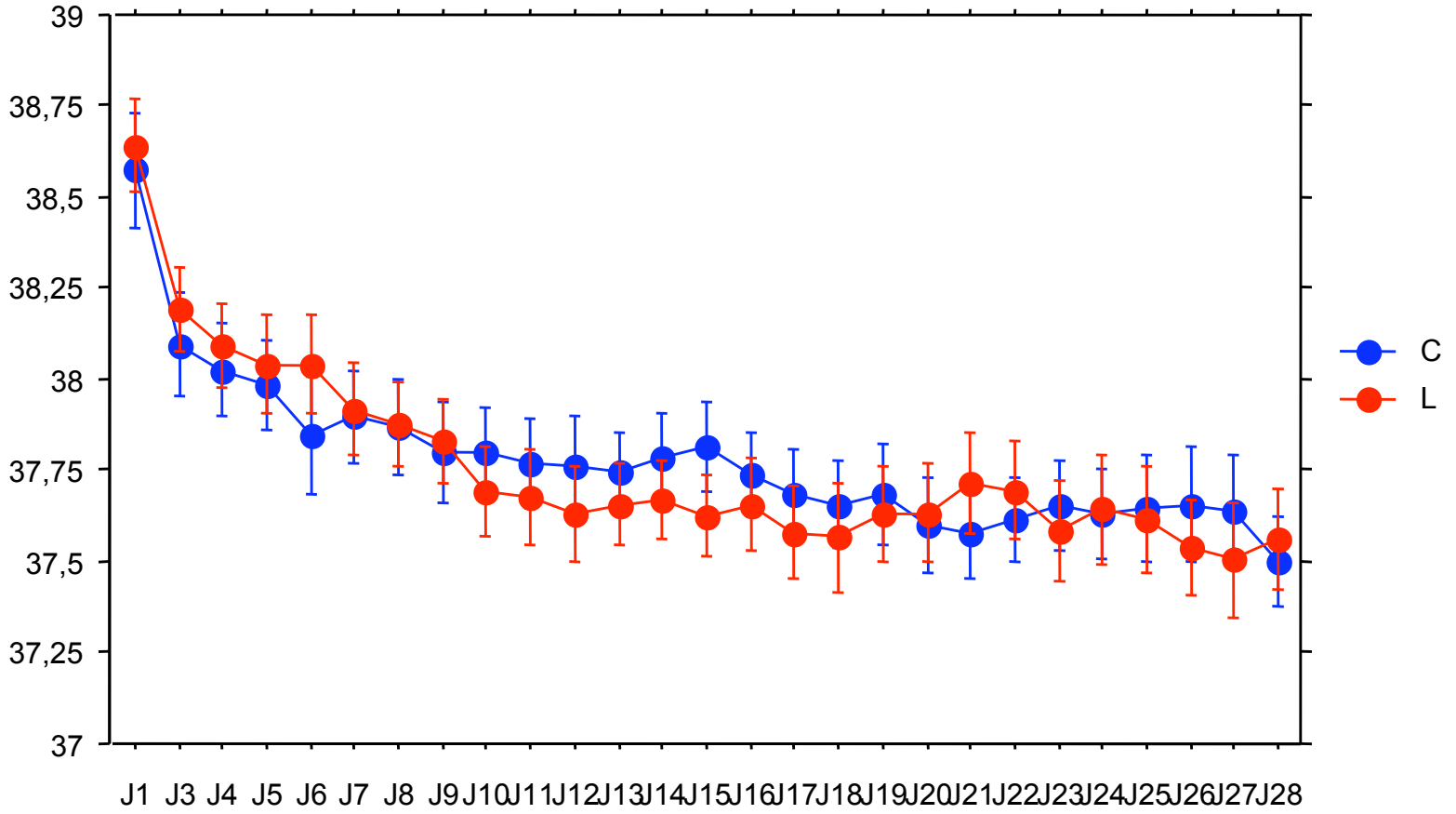
Results: secondary outcome measures

CRITERIA8-DAY	DIFFERENCE(95% CI)	No. of MV-free c	

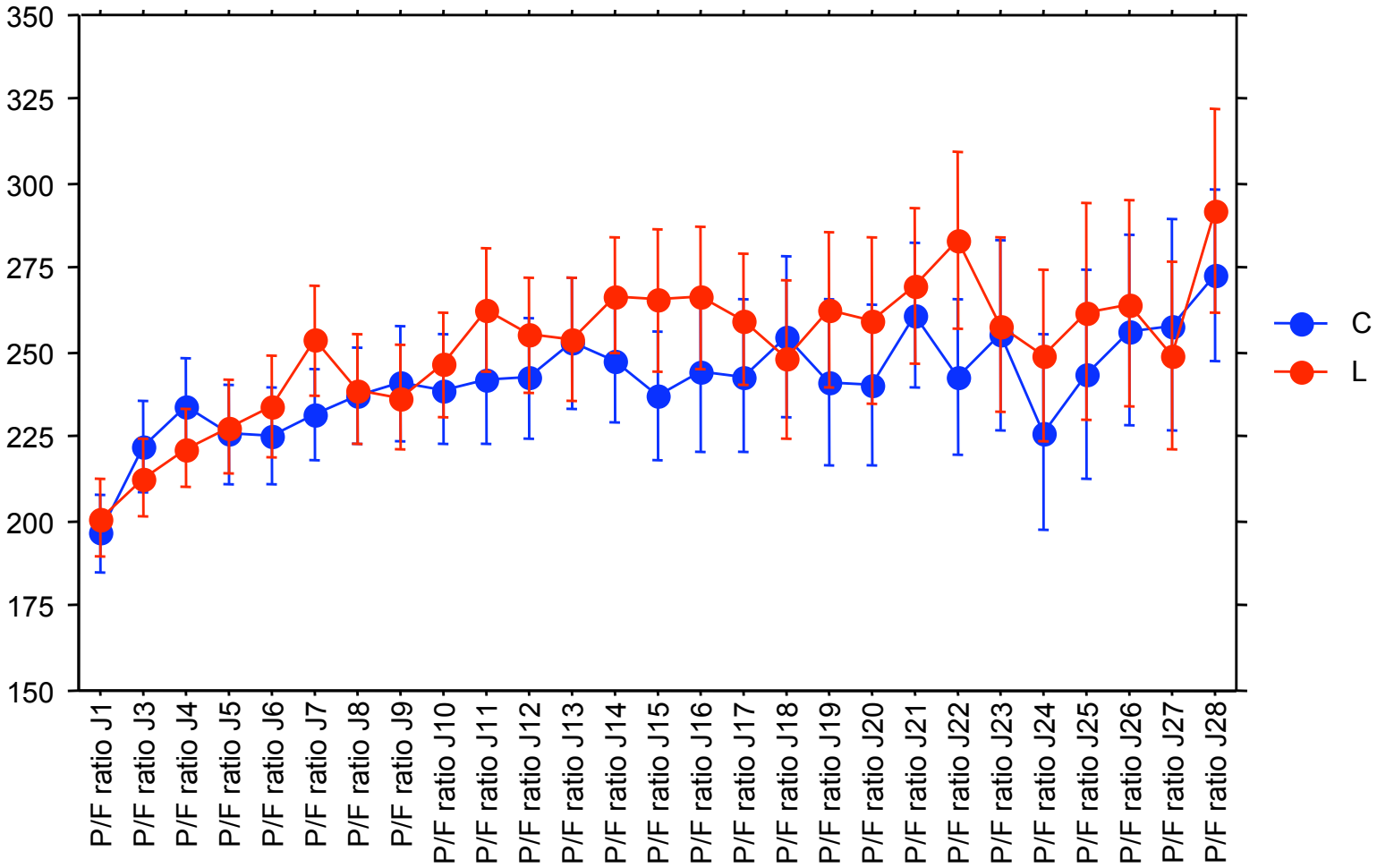
Changes in ODIN score from admission to day 28



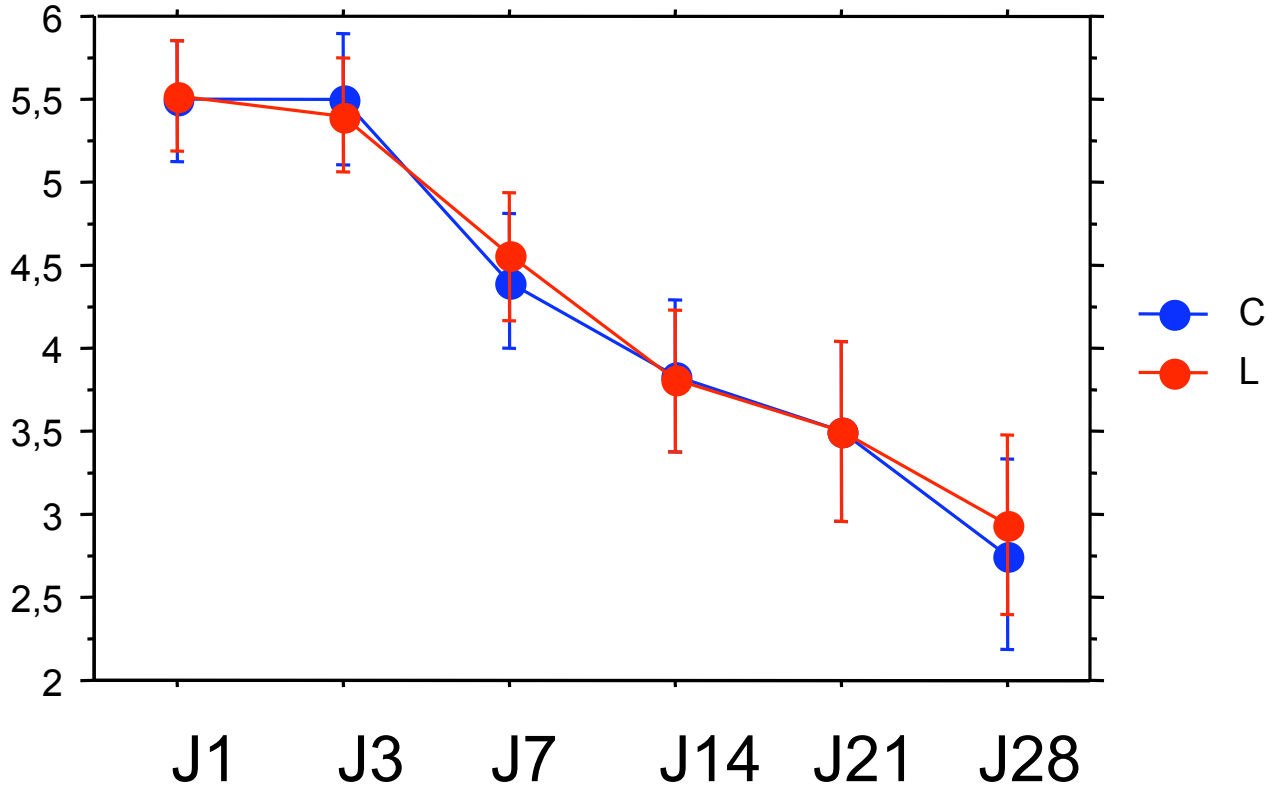
Changes in temperature from days 1 to 28



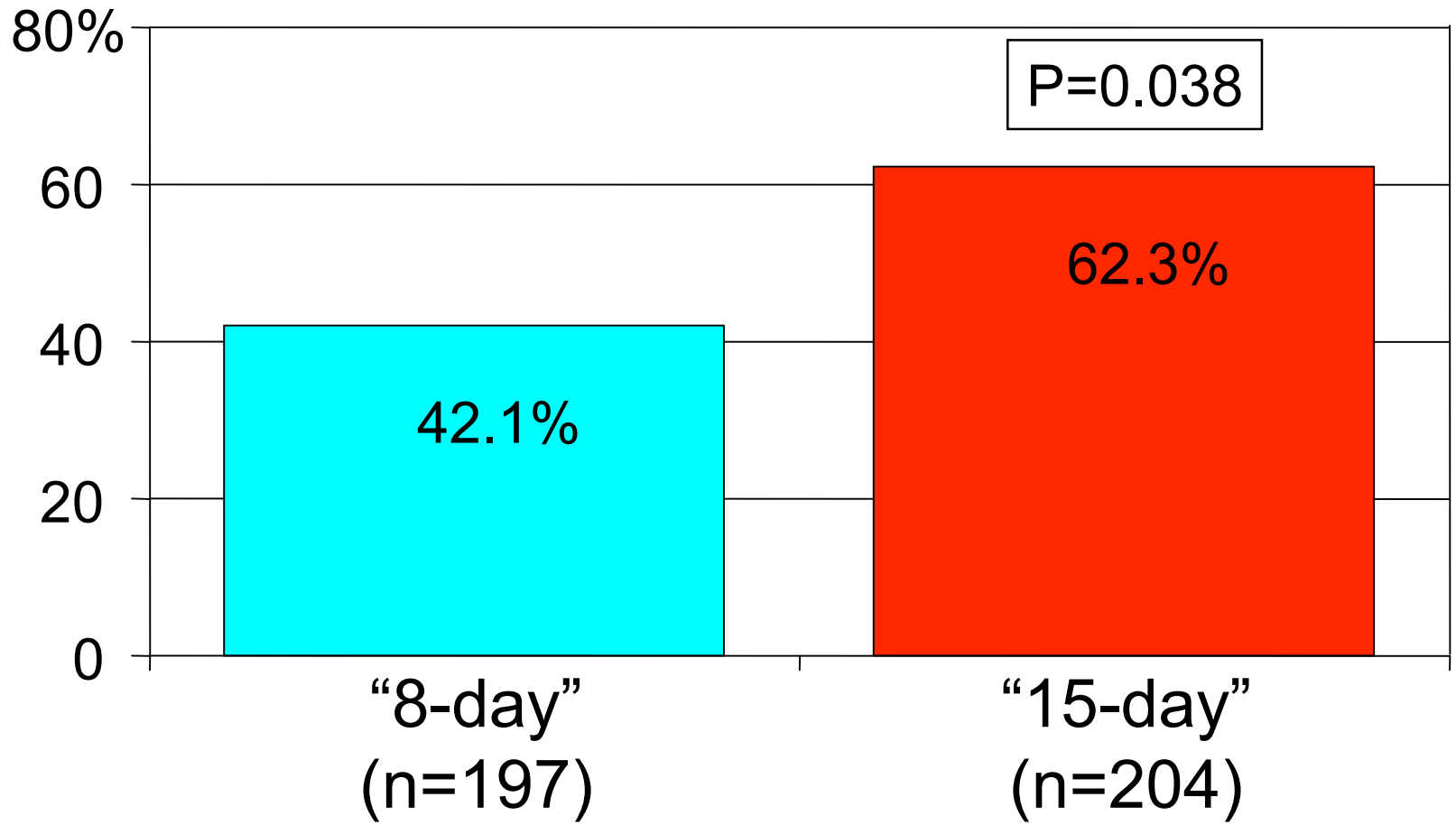
Changes in PaO_2/FIO_2 from days 1 to 28



Changes in radiologic score from days 1 to 28



Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence

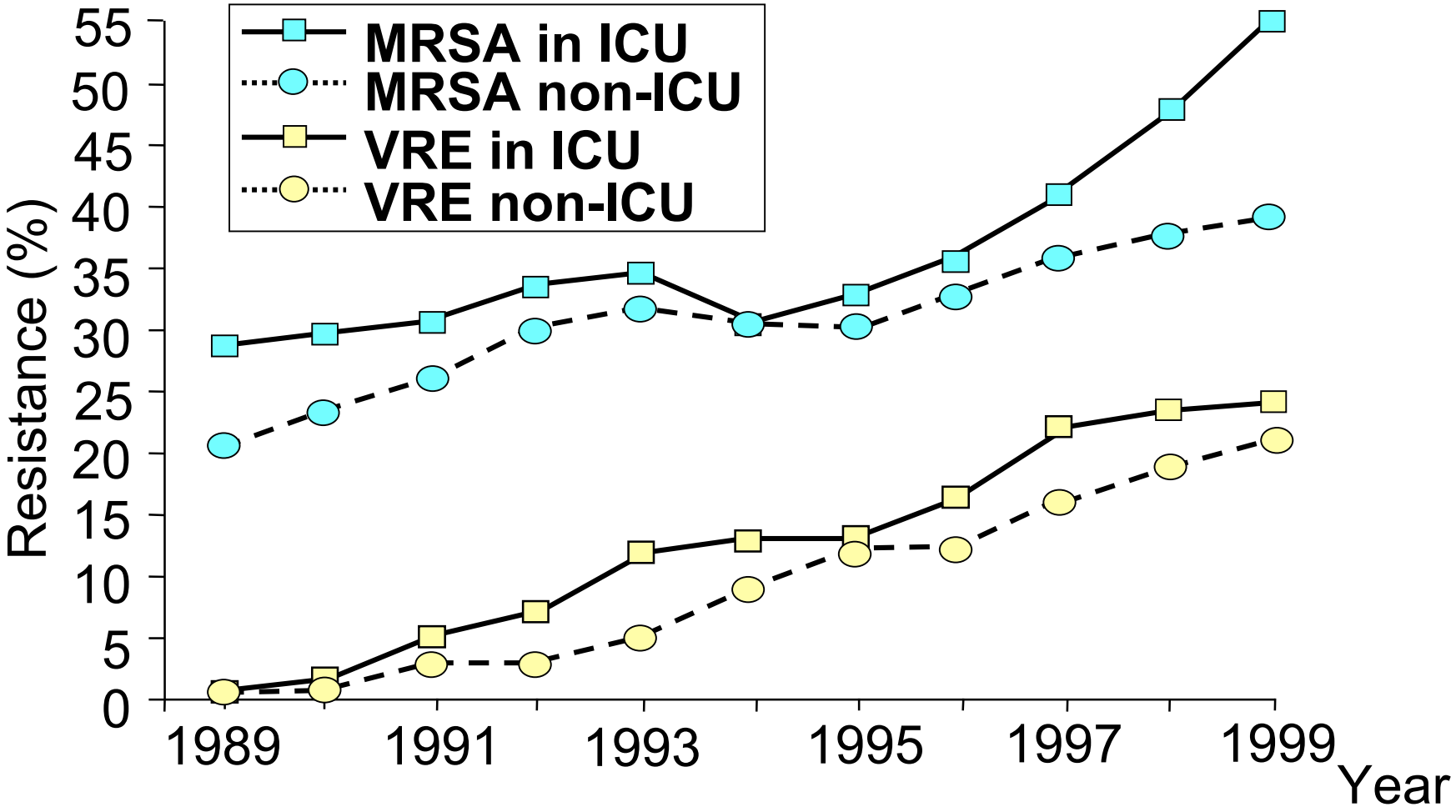


Summary:

- No evidence of a benefit could be documented when antimicrobial treatment was prolonged to 15 days in patients with VAP .
- A predefined short course of antibiotics could effectively reduce the exposition of ICU patients with VAP to any unnecessary antimicrobial therapy .
- Emergence of multiresistant pathogens for patients who had pulmonary infection recurrence was more frequent in patients treated with a long course of antibiotics than in those treated with a short course.

Increasing antibiotic resistance: Gram-positive organisms in the US

Harbarth S et al. Lancet Infect Dis 2001



Randomization:

- Randomization was centrally performed using an interactive voice system and stratified by center in blocks of 4.
- In order not to influence the choice of antimicrobial agents during the first week of treatment, the randomization assignment was concealed to the investigators until day 8.

Antimicrobial Treatment:

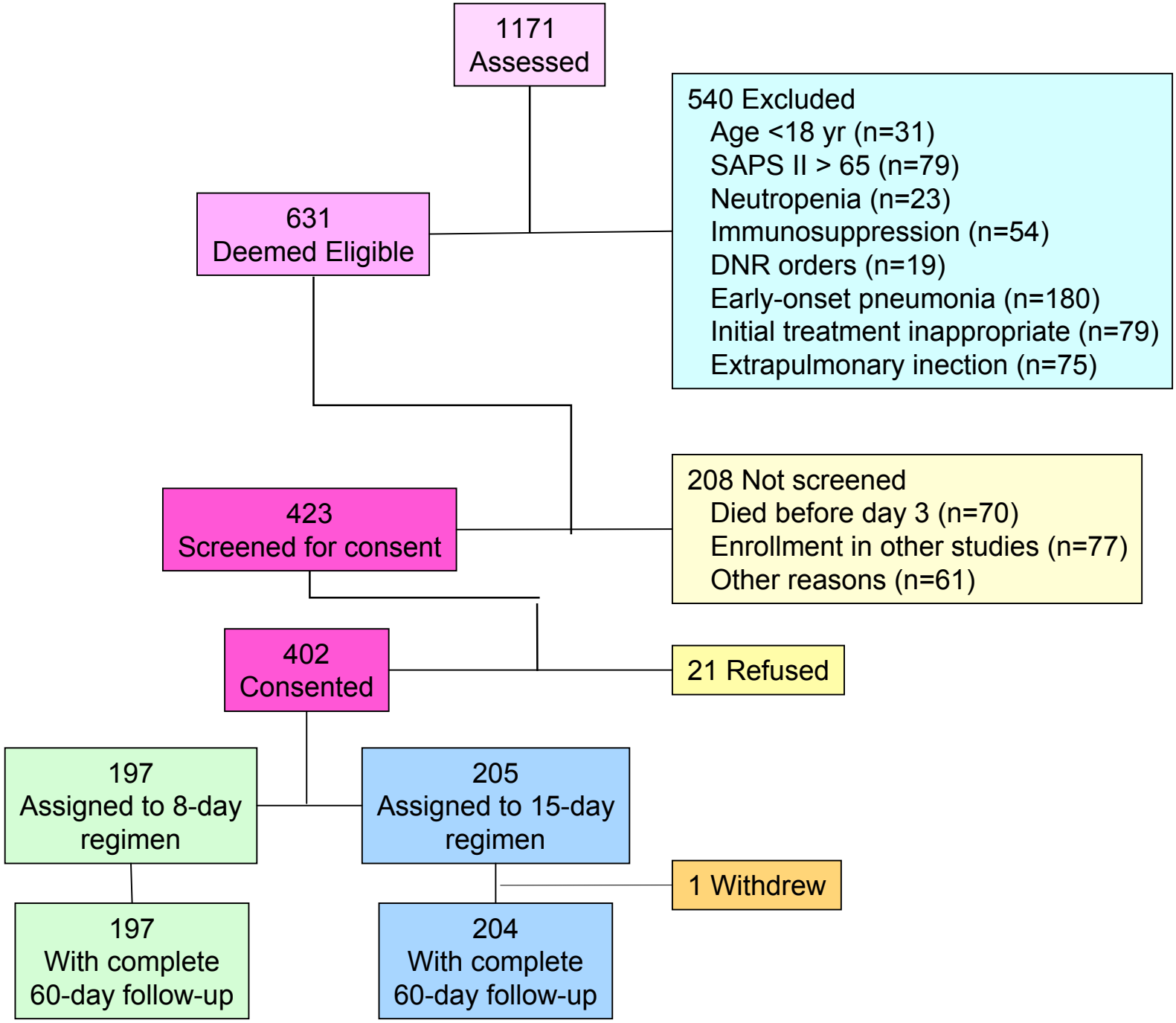
- Antibiotic treatments were left to the discretion of the treating physicians, including any adaptation considered necessary as a function of the definitive microbiological results identifying the pathogen(s) and their susceptibility patterns.
- Nevertheless, it was specified in the protocol that the initial antibiotic regimen i.e; before the susceptibility patterns of the responsible microorganisms were known should preferably combined at least an aminoglycoside or a fluoroquinolone plus a broad-spectrum betalactam antimicrobial agent.

Exclusion Criteria:

- Patients were excluded:
  - if they were pregnant;
  - were enrolled in another trial;
  - had little chance of survival, as defined by a SAPS II > 65;
  - had neutropenia (leukocytes < 1000/mm^3);
  - had concomitant acquired immunodeficiency syndrome;
  - had been treated with immunosuppressive treatment or long-term corticosteroid therapy (>0.5 mg/kg/day for >one month);
  - had a concomitant extra-pulmonary infection that required a prolonged (> 8 days) antimicrobial treatment;
  - had early-onset pneumonia and no prior antimicrobial therapy before the onset of infection
  - or their attending physician was unwilling to agree to the use of full life support.

Secondary Outcome Measures:

- the number of MV-free days;
- the number of organ failure-free days;
- the evolution of the SOFA and ODIN scores from days 1 to 28;
- the evolution of signs and symptoms potentially linked to pulmonary infection, including fever, leukocytosis, PaO_2/FIO_2 ratio and radiologic score;
- the length of stay in the ICU;
- the combined outcome of death, infection recurrence or prescription of a new antibiotic for any reason;
- the mortality at day 60;
- the in-hospital mortality;
- and the percentage of emerging multiresistant bacteria in case of pulmonary infection recurrence.


1171
Assessed
540 Excluded
Age <18 yr (n=31)
SAPS II > 65 (n=79)
Neutropenia (n=23)
Immunosuppression (n=54)
DNR orders (n=19)
Early-onset pneumonia (n=180)
Initial treatment inappropriate (n=79)
Extrapulmonary inection (n=75)
631
Deemed Eligible
208 Not screened
Died before day 3 (n=70)
Enrollment in other studies (n=77)
Other reasons (n=61)
423
Screened for consent
21 Refused
402
Consented
197
Assigned to 8-day regimen
205
Assigned to 15-day regimen
1 Withdrew
197
With complete 60-day follow-up
204
With complete 60-day follow-up