Duration of Therapy for HAP/VAP

- Proposed duration by ATS, 1995
  - Depending on severity of disease, time to clinical response, microorganisms
  - Long treatment: minimum 14 ~ 21 days
    - Multilobar involvement
    - Malnutrition
    - Cavitation
    - G(-) necrotizing pneumonia
    - Isolation of *P. aeruginosa* or *A. baumanii*
  - Short treatment: lasting 7 ~ 10 days
    - MSSA or *H. influenzae*

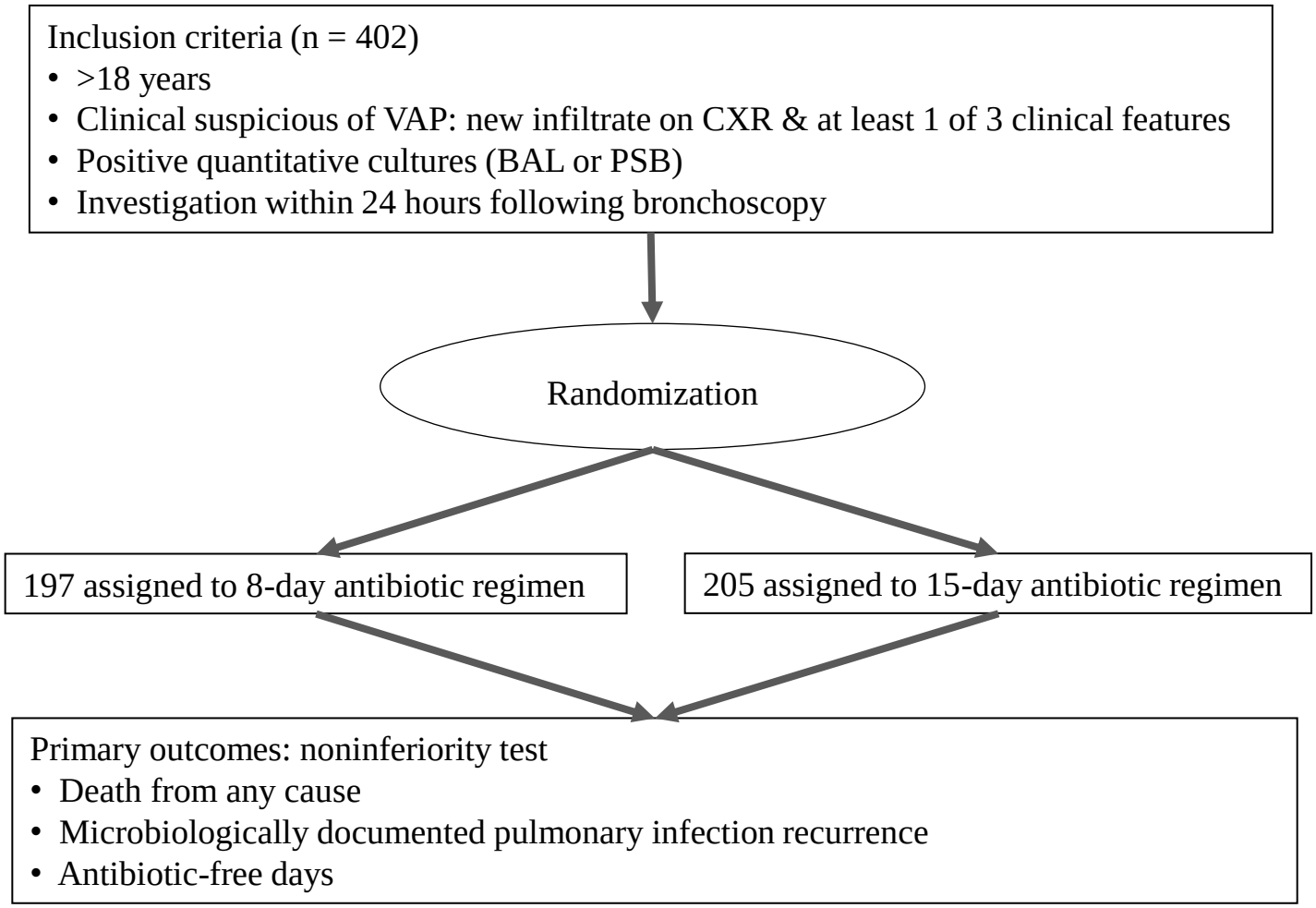
Am J Respir Crit Care Med 1995;153:1711

- Proposed duration by ATS, 2005
  - Efforts should be made to shorten the duration of therapy as short as 7 days
    - Not *P. aeruginosa* infection
    - Good clinical response with resolution of clinical features of infection

Am J Respir Crit Care Med 2005;171:388

8 days vs. 15 days Therapy for VAP

Multicenter RCT



JAMA 2003;290:2588

8 days vs. 15 days Therapy for VAP

Clinical Outcomes

Event	Mean (SD) 8-Day Regimen (n = 197)	Mean (SD) 15-Day Regimen (n = 204)	Mean Between-Group Difference (90% CI), %
No. of MV-free days, days 1 to 28			
All patients	8.7 (9.1)	9.1 (9.4)	–0.4 (–1.9 to 1.1)
Nonfermenting GNB*	8.1 (9.5)	6.6 (9.3)	1.4 (–1.3 to 4.2)
MRSA	6.1 (7.7)	7.4 (9.0)	–1.3 (–5.6 to 3.0)
Other bacteria	9.5 (9.0)	10.7 (9.2)	–1.2 (–3.2 to 0.8)
Length of ICU stay, d			
All patients	30.0 (20.0)	27.5 (17.5)	2.5 (–0.7 to 5.2)
Nonfermenting GNB	28.4 (18.4)	27.5 (17.8)	0.9 (–4.4 to 6.2)
MRSA	35.8 (19.4)	32.9 (17.9)	2.9 (–6.6 to 12.4)
Other bacteria	29.2 (18.3)	26.5 (17.2)	2.7 (–1.1 to 6.6)
	No. (%) of Patients		Risk Difference (90% CI), %
Unfavorable outcome*			
All patients	91 (46.2)	89 (43.6)	2.6 (–5.6 to 10.7)
Nonfermenting GNB	37/64 (57.8)	31/63 (49.2)	8.6 (–5.9 to 23.1)
MRSA	12/21 (57.1)	16/21 (76.2)	–19.0 (–42.5 to 4.4)
Other bacteria	42/112 (37.5)	42/120 (35)	2.5 (–7.9 to 12.9)
In-hospital mortality			
All patients	63 (32)	61 (29.9)	2.1 (–5.5 to 9.7)
Nonfermenting GNB	22/64 (34.4)	26/63 (41.3)	–6.9 (–21.0 to 7.2)
MRSA	11/21 (52.4)	9/21 (42.8)	9.5 (–15.7 to 34.8)
Other bacteria	30/112 (26.8)	26/120 (21.7)	5.1 (–4.1 to 14.4)

JAMA 2003;290:2588

8 days vs. 15 days Therapy for VAP

Pulmonary Infection Recurrence

Event	No./Total (%)		Between-Group Risk Difference (90% CI), %
	8-Day Regimen (n = 197)	15-Day Regimen (n = 204)	
Death from all causes*			
All patients	37/197 (18.8)	35/204 (17.2)	1.6 (–3.7 to 6.9)
Nonfermenting GNB†	15/64 (23.4)	19/63 (30.2)	–6.7 (–17.5 to 4.1)
MRSA	6/21 (28.6)	5/21 (23.8)	4.8 (–13.9 to 23.4)
Other bacteria	16/112 (14.3)	11/120 (9.2)	5.1 (–0.7 to 10.9)
Pulmonary infection recurrence*			
All patients	57/197 (28.9)	53/204 (26.0)	2.9 (–3.2 to 9.1)
Superinfection‡	39/197 (19.8)	38/204 (18.6)	1.2 (–4.3 to 6.6)
Relapse‡	33/197 (16.8)	23/204 (11.3)	5.5 (0.7 to 10.3)
Nonfermenting GNB†	26/64 (40.6)	16/63 (25.4)	15.2 (3.9 to 26.6)
Superinfection‡	13/64 (20.3)	8/63 (12.7)	7.6 (1.1 to 14.2)
Relapse‡	21/64 (32.8)	12/63 (19.0)	13.8 (7.8 to 19.7)
MRSA	7/21 (33.3)	9/21 (42.9)	–9.5 (–30.1 to 11.1)
Superinfection‡	6/21 (28.6)	5/21 (23.8)	4.8 (–8.8 to 18.3)
Relapse‡	3/21 (14.3)	4/21 (19.0)	–4.8 (–9.9 to 0.4)
Other bacteria	24/112 (21.4)	28/120 (23.3)	–1.9 (–9.5 to 5.6)
Superinfection‡	20/112 (17.9)	25/120 (20.8)	–3.0 (–8.2 to 2.2)
Relapse‡	9/112 (8.0)	7/120 (5.8)	2.2 (–1.3 to 5.7)

JAMA 2003;290:2588

Early Antibiotics Discontinuation in VAP
Single Center RCT

- Discontinuation policy
  - Confirmed noninfectious etiology of infiltration on CXR
  - Resolution of clinical parameter of VAP

▶ Duration of antibiotics: 6.0 ± 4.9 days vs. 8.0 ± 5.6 days, p = 0.001

Pathogen	Discontinuation Group (n = 150)	Conventional Group (n = 140)	p Value
Methicillin-resistant *S aureus*	31 (20.7)	26 (18.6)	0.654
Methicillin-sensitive *S aureus*	16 (10.7)	19 (13.6)	0.448
P aeruginosa	17 (11.3)	14 (10.0)	0.713
Acinetobacter species	0 (0.0)	1 (0.7)	0.483
Other Gram-negative bacteria	35 (23.3)	27 (19.3)	0.401
Aspergillus/Candida species	15 (10.0)	12 (8.6)	0.676
Other pathogens	17 (11.3)	22 (15.7)	0.275
No pathogens isolated	30 (20.0)	35 (25.0)	0.308
Multiple pathogens	10 (6.7)	14 (10.0)	0.303

*Data are presented as No. (%).

Outcomes	Discontinuation Group (n = 150)	Conventional Group (n = 140)	p Value
Hospital mortality	48 (32.0)	52 (37.1)	0.357
Hospital length of stay, d	15.7 ± 18.2	15.4 ± 15.9	0.865
ICU length of stay, d	6.8 ± 6.1	7.0 ± 7.3	0.798
Duration of ventilation, d	5.4 ± 5.7	5.7 ± 7.1	0.649
Subsequent infection	56 (37.3)	46 (32.9)	0.425

*Data are presented as No. (%) or mean ± SD.

Chest 2004;125:1791

Short- vs Long-Duration Antibiotics for VAP

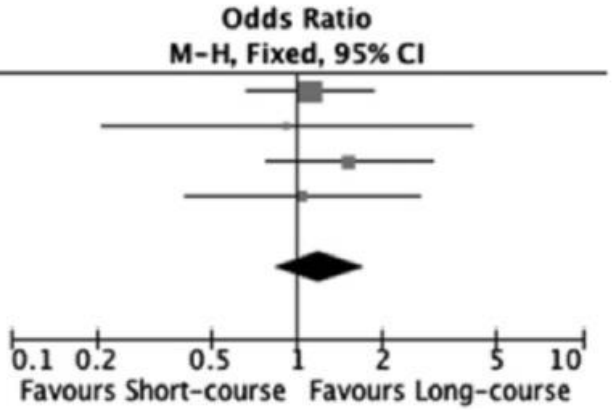
Meta-analysis

ORs of mortality

Study or Subgroup	Short-course Events	Short-course Total	Long-course Events	Long-course Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chastre et al	37	197	35	204	51.6%	1.12 [0.67, 1.86]	2003
Fekih Hassen et al	5	14	6	16	6.7%	0.93 [0.21, 4.11]	2009
Kollef et al	26	115	18	112	26.1%	1.53 [0.78, 2.97]	2012
Capellier et al	10	116	9	109	15.7%	1.05 [0.41, 2.69]	2012
Total (95% CI)		**442**		**441**	**100.0%**	**1.20 [0.84, 1.72]**	
Total events	78		68				

Heterogeneity: $Chi^2 = 0.77$, $df = 3$ ($P = 0.86$); $I^2 = 0\%$

Test for overall effect: $Z = 0.99$ ($P = 0.32$)

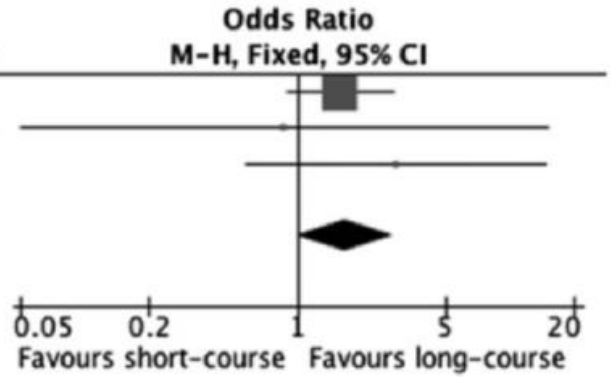


ORs of relapses

Study or Subgroup	Short-course Events	Short-course Total	Long-course Events	Long-course Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Chastre et al	33	197	23	204	86.4%	1.58 [0.89, 2.81]	2003
Fekih Hassen et al	1	16	1	14	4.6%	0.87 [0.05, 15.28]	2009
Capellier et al	6	116	2	109	9.0%	2.92 [0.58, 14.78]	2012
Total (95% CI)		**329**		**327**	**100.0%**	**1.67 [0.99, 2.83]**	
Total events	40		26				

Heterogeneity: $Chi^2 = 0.69$, $df = 2$ ($P = 0.71$); $I^2 = 0\%$

Test for overall effect: $Z = 1.91$ ($P = 0.06$)



Chest 2013;144:1759

Meta-analysis with 6 RCTs

Should short-course antibiotic therapy versus prolonged-course antibiotic therapy be used in critically ill patients with hospital-acquired pneumonia?

Patient or population: hospital-acquired pneumonia
Settings: intensive care
Intervention: short-course antibiotic therapy
Comparison: prolonged-course antibiotic therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Prolonged-course antibiotic therapy	Short-course antibiotic therapy			
Mortality Follow-up: 28 days	**175 per 1000**	**201 per 1000** (141 to 277)	**OR 1.18** (0.77 to 1.8)	598 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
Mortality NF-GNB Follow-up: 28 days	**265 per 1000**	**255 per 1000** (123 to 450)	**OR 0.95** (0.39 to 2.27)	179 (2 studies)	⊕⊕⊖⊖ **low**[1,2]
Mortality MRSA Follow-up: 28 days	**238 per 1000**	**286 per 1000** (91 to 614)	**OR 1.28** (0.32 to 5.09)	42 (1 study)	⊕⊕⊕⊖ **moderate**[1]
Recurrence of pneumonia Clinical and/or microbiological criteria	**180 per 1000**	**237 per 1000** (171 to 318)	**OR 1.41** (0.94 to 2.12)	733 (19 studies)	⊕⊕⊖⊖ **low**[1,3]
Recurrence of pneumonia NF-GNB Clinical and/or microbiological criteria	**247 per 1000**	**417 per 1000** (272 to 577)	**OR 2.18** (1.14 to 4.16)	176 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
Recurrence of pneumonia MRSA Clinical and/or microbiological criteria	**370 per 1000**	**479 per 1000** (66 to 920)	**OR 1.56** (0.12 to 19.61)	49 (2 studies)	⊕⊕⊕⊖ **moderate**[1]
28-day antibiotic-free days Follow-up: 28 days	The mean 28-day antibiotic free days in the intervention groups was **4.02 higher** (2.26 to 5.78 higher)			431 (2 studies)	⊕⊕⊖⊖ **low**[1,4]

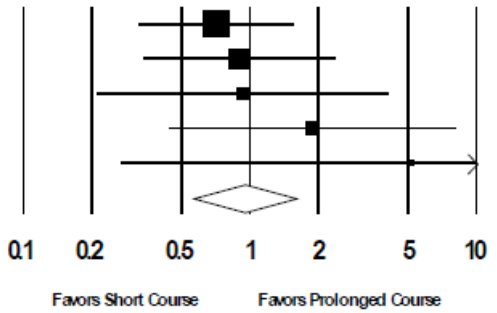
Cochrane Database Syst Rev 2015(8):CD007577.

Short Course in NF-GNR VAP

ATS/IDSA Guideline, 2016

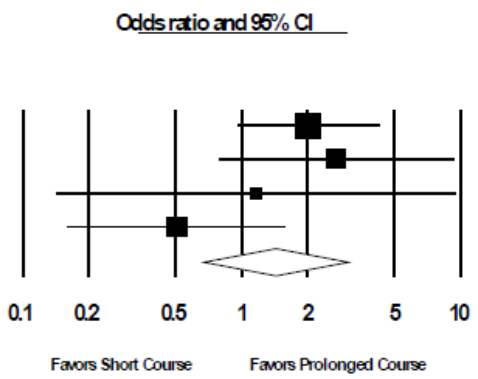
All-Cause Mortality: NF-GNR Only/VAP and Randomized Studies: Short vs. Prolonged Course

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Death / Total: Short Fixed Course	Death / Total: Prolonged Course	Death / Total: Total
Chastre 2003	0.71	0.32	1.56	0.39	15 / 64	19 / 63	34 / 127
Medina 2007	0.90	0.33	2.41	0.83	11 / 40	11 / 37	22 / 77
Fekih-Hassen 2009	0.93	0.21	4.11	0.92	5 / 14	6 / 16	11 / 30
Kollef 2012	1.89	0.44	8.18	0.39	8 / 32	3 / 20	11 / 52
Capellier 2012	5.16	0.26	100.52	0.28	4 / 41	0 / 21	4 / 62
	0.94	0.56	1.59	0.83	43 / 191	39 / 157	82 / 348



Pneumonia Recurrence: NF-GNR Only/VAP and Randomized Studies: Short vs. Prolonged Course

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Recurrence / Total: Short Fixed Course	Recurrence / Total: Prolonged Course	Recurrence / Total: Total
Chastre 2003 (France)	2.01	0.94	4.28	0.07	26 / 64	16 / 63	42 / 127
Medina 2007 (Uruguay)	2.72	0.78	9.52	0.12	12 / 27	5 / 22	17 / 49
Fekih-Hassen 2009 (Tunisia)	1.17	0.14	9.59	0.89	2 / 14	2 / 16	4 / 30
Capellier 2012 (France)	0.50	0.16	1.60	0.25	13 / 42	8 / 17	21 / 59
	1.42	0.66	3.04	0.37	53 / 147	31 / 118	84 / 265



Clin Infect Dis 2016;63(5):e61

Short Course Therapy for P. aeruginosa VAP
Open-Label Non-Inferiority Trial, iDIAPASON

Primary outcome and its components, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (90% CI)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in ITT population—no. (%)	25/98 (25.5)	31/88 (35.2)	9.7% (0–21.2%)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in PP population—no. (%)	22/80 (27.5)	29/72 (40.3)	12.8% (0–25.6%)
PA-VAP recurrence rate during hospitalization in the ICU in ITT population—no. (%)	9/98 (9.2)	15/88 (17)	7.9% (0–16.8%)

PA-VAP, pseudomonas aeruginosa ventilator-associated pneumonia; ICU, Intensive Care Unit; PP, per protocol; ITT, intention-to-treat

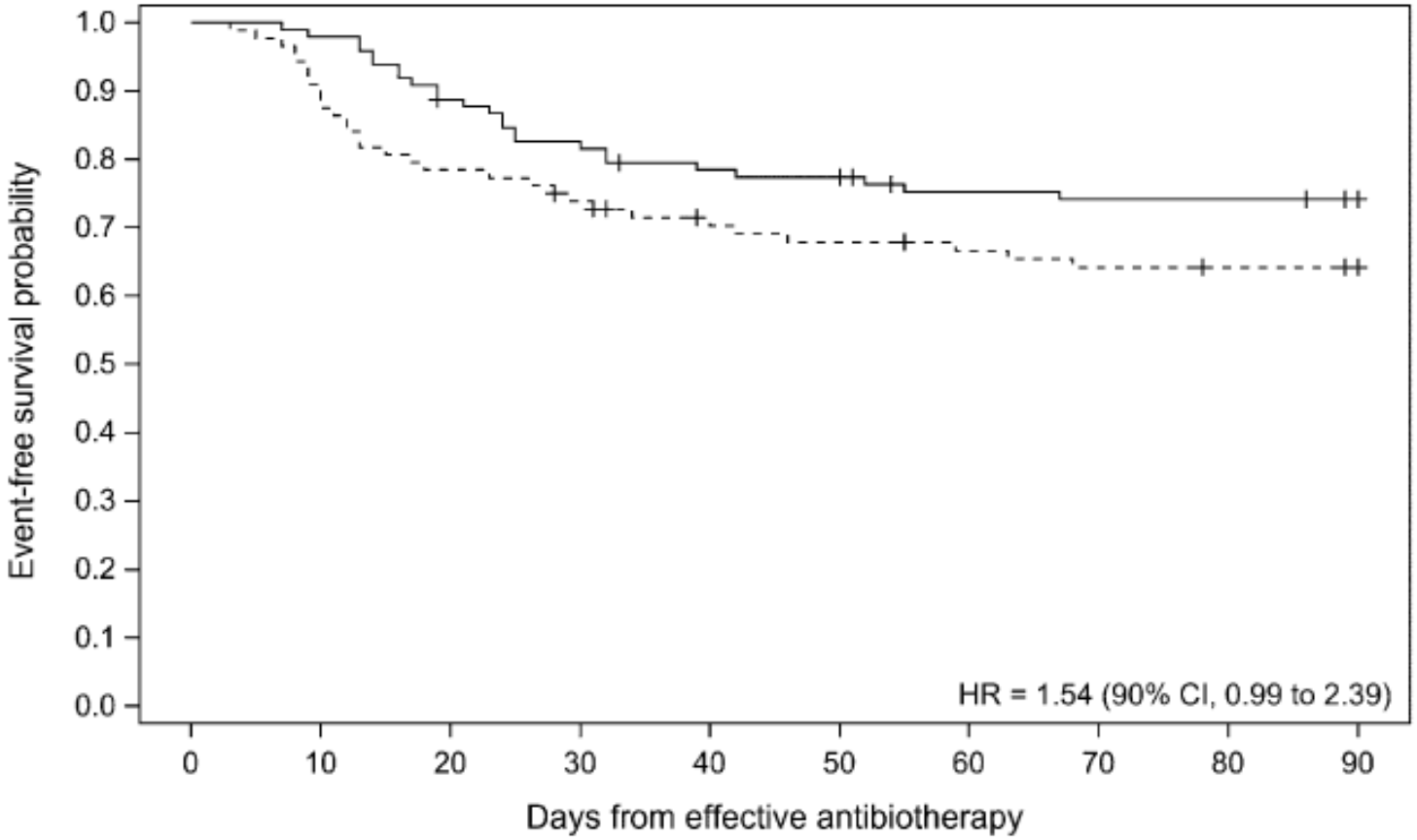
Secondary outcomes, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (95% CI)
Duration of mechanical ventilation, days[a]	25 (15.5–35)	22 (12–41)	− 3 (− 9 to 5)
Duration of ICU stay, days	34 (23–56)	34 (20–54)	0 (− 7 to 6)
Exposure to antibiotics during ICU stay, days	23 (15–34)	18 (11.5–28.5)	− 5 (− 9 to 0)
Number of extra pulmonary infections during ICU stay[a]	1 (0–2)	1 (0–2)	0 (− 1 to 1)
Acquisition of MDR pathogens during ICU stay—no. (%)	24/97 (24.7)	17/84 (20.2)	− 4.5% (− 16.8 to 8.3%)

Intensive Care Med 2022 doi: 10.1007/s00134-022-06690-5.

Short Course Therapy for P. aeruginosa VAP

Event Free Survival Curves



No at risk										
15 days	98	96	86	80	75	74	69	68	68	60
8 days	88	80	69	64	59	56	54	52	51	48

Intensive Care Med 2022 doi: 10.1007/s00134-022-06690-5.

Recommendation

- In summary,
  - No benefit to prolonged courses of antibiotic therapy (longer than 7-10 days) for HAP/VAP.
  - Potential risk of relapse of VAP associated with non-fermenting Gram-negative bacilli.

▶ In patients with HAP/VAP, the duration of antibiotic therapy can be shortened to 7-10 days, but longer courses of antibiotics may be needed in patients with VAP of non-fermenting Gram-negative bacilli, especially in *P. aeruginosa*.