Pneumonia review

2018.04.14.

고대구로병원 호흡기내과 오지연

- CAP:
  - Antibiotics duration (JAMA Intern Med. 2016;176(9):1257-1265)
  - Steroid in CAP (Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720)
  - (Clin Infect Dis. 2018 Jan 18;66(3):346-354)
  - Risk of heart failure (BMJ. 2017;356:j413)

- HAP/VAP:
  - ATS guideline 2016 (Clin Infect Dis. 2016; 63: e61–e111)
  - ERS guideline 2017 (Eur Respir J. 2017; 50: 1700582)

CAP

JAMA Intern Med. 2016;176(9):1257-1265

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia
A Multicenter Randomized Clinical Trial

Ane Uranga, MD; Pedro P. España, MD; Amaia Bilbao, MSc, PhD; Jose María Quintana, MD, PhD; Ignacio Arriaga, MD; Maider Intxausti, MD; Jose Luis Lobo, MD, PhD; Laura Tomás, MD; Jesus Camino, MD; Juan Nuñez, MD; Alberto Capelastegui, MD, PhD

JAMA Intern Med. 2016;176(9):1257-1265

- Multicenter, noninferiority randomized clinical trial
- From January 1, 2012, through August 31, 2013 in Spain.
- A total of 312 hospitalized patients diagnosed as having CAP
- Intervention group vs. control group
- Primary outcome: Clinical success rate at days 10 and 30
  CAP-related symptoms at days 5 and 10

ATS/IDSA 2007 guideline

Duration of Antibiotic Therapy

32. Patients with CAP should be treated for a minimum of 5 days (level I evidence), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability (table 10) before discontinuation of therapy (level II evidence). (Moderate recommendation.)

Table 10. Criteria for clinical stability.

Temperature ≤37.8°C
Heart rate ≤100 beats/min
Respiratory rate ≤24 breaths/min
Systolic blood pressure ≥90 mm Hg
Arterial oxygen saturation ≥90% or pO_2 ≥60 mm Hg on room air
Ability to maintain oral intake[a]
Normal mental status[a]

NOTE. Criteria are from [268, 274, 294]. pO_2, oxygen partial pressure.

[a] Important for discharge or oral switch decision but not necessarily for determination of nonresponse.

JAMA Intern Med. 2016;176(9):1257-1265

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	*P* Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)[a]			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%)[a]			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

Abbreviation: CAP, community-acquired pneumonia.

[a] Percentages exclude patients with missing data. In the intent-to-treat population, the percentage of missing data for each variable was as follows: clinical success at day 10, 1.9%; clinical success at day 30, 0.9%; CAP symptom questionnaire score at day 5, 3.8%; and CAP symptom questionnaire score at day 10, 4.4%. In the per-protocol population, the percentage of missing data was as follows: clinical success at day 10, 2.1%; clinical success at day 30, 1.0%; CAP symptom questionnaire score at day 5, 3.1%; and CAP symptom questionnaire score at day 10, 3.8%.

[b] On the CAP symptom questionnaire, which is a specific and validated patient-reported outcome measure based on 18 items, higher scores indicated more severe CAP-related symptoms (range, 0-90).

JAMA Intern Med. 2016;176(9):1257-1265

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02

- IDSA/ATS recommendations for duration of antibiotic treatment based on clinical stability criteria (minimum 5 days) can be safely implemented in hospitalized patients with CAP

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720.

Cochrane Library

Cochrane Database of Systematic Reviews

Corticosteroids for pneumonia (Review)

Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M

17 RCTs comprising a total of 2264 participants
Adults: 13 RCTs, ~ 2000 patients

JAMA. 2015;313(7):677-686

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Corticosteroids on Treatment Failure Among Hospitalized Patients With Severe Community-Acquired Pneumonia and High Inflammatory Response

A Randomized Clinical Trial

Antoni Torres, MD, PhD; Oriol Sibila, MD, PhD; Miquel Ferrer, MD, PhD; Eva Polverino, MD, PhD; Rosario Menendez, MD, PhD; Josep Mensa, MD, PhD; Albert Gabarrús, MSc; Jacobo Sellarés, MD, PhD; Marcos I. Restrepo, MD, MSc; Antonio Anzueto, MD, PhD; Michael S. Niederman, MD; Carles Agustí, MD, PhD

- Severe CAP and a high inflammatory response (CRP >150 mg/L)
- IV methylprednisolone 0.5 mg/kg/12 hours vs placebo 5일, 36 시간 이내 투여
- Less treatment failure
  - Steroid group (8 patients [13%]) vs placebo group (18 patients [31%]),
  - OR, 0.34 [95% CI, 0.14 to 0.87]; P = 0.02

- In-hospital mortality did not differ between the 2 groups

Lancet 2015; 385: 1511–18

Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial

Claudine Angela Blum, Nicole Nigro*, Matthias Briel, Philipp Schuetz, Elke Ullmer, Isabelle Suter-Widmer, Bettina Winzeler, Roland Bingisser, Hanno Elsaesser, Daniel Drozdov, Birsen Arici, Sandrine Andrea Urwyler, Julie Refardt, Philip Tarr, Sebastian Wirz, Robert Thomann, Christine Baumgartner, Hervé Duplain, Dieter Burki, Werner Zimmerli, Nicolas Rodondi, Beat Mueller, Mirjam Christ-Crain*

- CAP
- Prednisone 50 mg daily vs placebo for 7 days
- Shorter time to clinical stability
  - Steroid group (3·0 days) than in the placebo group (4·4 days; HR 1·33, 95% CI 1·15–1·50, P<0·0001)

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with corticosteroids				
Mortality - adults	Study population		RR 0.66 (0.47 to 0.92)	1863 (11 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	82 per 1000	53 per 1000 (38 to 74)				
Mortality - adults - severe CAP	Study population		RR 0.58 (0.40 to 0.84)	995 (9 RCTs)	⊕⊕⊕◯ MODERATE [1]	
	131 per 1000	76 per 1000 (52 to 110)				
Mortality - adults - non-severe CAP	Study population		RR 0.95 (0.45 to 2.00)	868 (4 RCTs)	⊕⊕⊕◯ MODERATE [2]	
	29 per 1000	28 per 1000 (13 to 58)				

Death from any cause, radiographic progression or clinical instability at day 5-8

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with corticosteroids				
Early clinical failure - adults	Study population		RR 0.40 (0.23 to 0.70)	1324 (6 RCTs)	⊕⊕⊕◯ MODERATE [34]	
	373 per 1000	149 per 1000 (86 to 261)				
Early clinical failure - adults - severe CAP	Study population		RR 0.32 (0.15 to 0.70)	419 (5 RCTs)	⊕⊕⊕⊕ HIGH [5]	
	422 per 1000	135 per 1000 (63 to 296)				
Early clinical failure - adults - non-severe CAP	Study population		RR 0.68 (0.56 to 0.83)	905 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	352 per 1000	240 per 1000 (197 to 292)				

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Time to clinical cure - adults	9	1322	Mean Difference (IV, Random, 95% CI)	-1.83 [-2.45, -1.21]
9 Time to clinical cure - children	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Bacterial pneumonia	3	225	Mean Difference (IV, Random, 95% CI)	-1.57 [-2.55, -0.60]
9.2 Viral pneumonia	1	41	Mean Difference (IV, Random, 95% CI)	1.70 [-2.50, 5.90]
10 Need for mechanical ventilation - adults	4	1030	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.20, 0.77]
11 Development of shock - adults	6	415	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.09, 0.34]
12 Need for ICU transfer - adults	4	1164	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.45, 1.18]
13 Length of hospitalisation - adults	9	1658	Mean Difference (IV, Random, 95% CI)	-2.91 [-4.92, -0.89]
14 Length of ICU stay - adults	8	342	Mean Difference (IV, Fixed, 95% CI)	-1.88 [-2.96, -0.81]

Cochrane Database Syst Rev. 2017 Dec 13;12:CD007720.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Pneumonia complications - adults + children	9	1632	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.40, 0.84]
17 Secondary infections - adults	7	1533	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.73, 1.93]
18 Secondary infections - children	3	225	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
18.1 Bacterial pneumonia	3	225	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
19 Any adverse events - adults	3	1028	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.99, 1.47]
20 Hyperglycaemia - adults	7	1578	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.38, 2.14]
21 Gastrointestinal bleeding - adults	7	1190	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.40, 2.05]
22 Neuropsychiatric side effects - adults	4	1149	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.70, 5.42]
23 Adverse cardiac events - adults	5	1249	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.32, 1.13]

- Corticosteroid therapy reduced mortality and morbidity in adults with severe CAP
- Corticosteroid therapy reduced morbidity, but not mortality, for adults with non-severe CAP
- Corticosteroid therapy was associated with more adverse events, especially hyperglycemia, but the harms did not seem to outweigh the benefits.

Clin Infect Dis. 2018 Jan 18;66(3):346-354

Clinical Infectious Diseases

MAJOR ARTICLE

Corticosteroids in Patients Hospitalized With Community-Acquired Pneumonia: Systematic Review and Individual Patient Data Metaanalysis

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Individual patient data meta-analysis
1506 individual patients in 6 trials

Clin Infect Dis. 2018 Jan 18;66(3):346-354

Table 2. Baseline Characteristics of the Pooled 1506 Patients from 6 Randomized Clinical Trials on Adjunctive Corticosteroid Therapy in Community-Acquired Pneumonia

Characteristic	Corticosteroid (N = 748)	Placebo (N = 758)
Age (y), median (IQR)	71 (56–81)	70 (55–81)
Female sex, no. (%)	318 (42.5)	294 (38.8)
Current smoker, no. (%)	199 (27.8)	189 (26.4)
Antibiotic treatment before hospitalization, no. (%)	227 (30.5)	233 (30.9)
Immediate admission to intensive care unit, no. (%)	70 (9.4)	77 (10.2)
Clinical parameters		
Days with symptoms, median (IQR)	4 (2–7)	4 (2–7)
Temperature (°C), median (IQR)	37.8 (37.1–38.6)	37.9 (37.1–38.6)
Systolic blood pressure (mmHg), median (IQR)	126 (112–141)	126 (112–141)
Heart rate (beats per min), median (IQR)	90 (78–105)	90 (77–106)
Respiratory rate (breaths per min)	24 (19–30)	24 (19–30)
SaO_2 (%), median (IQR)	94 (92–96)	95 (92–97)
Confusion, no. (%)	70 (9.5)	70 (9.5)
Laboratory values		
C-reactive protein (mg/L), median (IQR)	191 (93–290)	183 (84–292)
White-blood-cell count (10^9 cells/L), median (IQR)	12.7 (9.3–16.7)	12.6 (9.0–16.7)
Glucose (mmol/L), median (IQR)	6.9 (5.9–8.4)	6.8 (5.9–8.2)
Positive blood cultures (bacterial community-acquired pneumonia), no. (%)	89 (12.8)	87 (12.5)
PSI score[a]		
class I, ,no. (%)	83 (11.1)	79 (10.4)
class II, no. (%)	132 (17.7)	135 (17.8)
class III, no. (%)	127 (17.0)	172 (22.7)
class IV, no. (%)	285 (38.1)	250 (33.0)
class V, no. (%)	121 (16.2)	122 (16.1)
Total PSI score (points), median (IQR)	95 (68–120)	90 (66–114)
Identified pathogen		
Streptococcus pneumonia	171 (22.9)	154 (20.3)
Other pathogen[b]	146 (19.5)	184 (24.3)
No pathogen found	431 (57.6)	420 (55.4)
Number of systemic inflammatory response syndrome criteria		
0, no. (%)	32 (4.5)	19 (2.6)
1, no. (%)	137 (19.1)	151 (20.4)
2, no. (%)	246 (34.2)	239 (33.2)
3, no. (%)	213 (29.6)	218 (30.2)
4, no. (%)	91 (12.7)	94 (13.0)
Comorbidities		
Diabetes mellitus (any type), no. (%)	123 (16.4)	130 (17.2)
Insulin treatment, no. (%)	57 (7.7)	46 (6.2)
Chronic obstructive pulmonary disease, no. (%)	125 (16.7)	112 (14.8)
Chronic heart failure, no. (%)	134 (17.9)	126 (16.7)
Cerebrovascular disease, no. (%)	86 (11.5)	78 (10.3)
Renal disease, no. (%)	153 (20.5)	139 (18.4)
Active neoplastic disease, no. (%)	46 (6.2)	49 (6.5)
Liver disease, no. (%)	22 (3.0)	15 (2.0)
Coinfections at admission, no. (%)	48 (7.1)	50 (7.3)

Abbreviations: IQR, interquartile range; PSI, pneumonia severity index.

[a]PSI is a clinical prediction rule to calculate the probability of morbidity and mortality among patients with community-acquired pneumonia. PSI risk class I: aged ≤50 years and no risk factors; II: <70; III: 71–90; IV: 91–130; V: >130 points.

[b]Of 330 patients with other identified pathogens, there were, for example, 45 (13.6%) with *Legionella* species, 31 (9.4%) with influenza virus A or B, 29 (8.8%) with *Haemophilus influenzae*, 29 (8.8%) with *Coxiella burnetii*, 25 (7.6%) with *Mycoplasma pneumoniae*, and 18 (5.5%) with *Chlamydophilia* species.

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Table 3. Primary and Secondary Outcomes at 30 days After Randomization Using Random Intercepts for Included Trials

Outcome	Corticosteroid (n = 748)	Placebo (n = 758)	Intention-to-Treat Regression analysis, OR or Coefficient (95% Confidence Interval), *P* Value
Primary			
All-cause mortality, no. (%)	37 (5.0)	45 (5.9)	OR 0.75 (0.46 to 1.21), *P* = .24
Secondary			
Secondary intensive care unit admission, no. (%)[a]	38 (5.6)	43 (6.3)	OR 0.74 (0.45 to 1.21), *P* = .23
Length of hospital stay, days	7.0 (5.0–11.0)	8.0 (5.0–12.0)	–1.15 days (–1.75 to –0.55), *P* < .001
Time to clinical stability, days[b]	3.0 (2.0–5.4)	4.0 (2.5–7.0)	–1.03 days (–1.62 to –0.43), *P* = .001
Intravenous antibiotic treatment, days[c]	4.0 (3.0–6.0)	5.0 (3.0–7.0)	–0.62 days (–1.07 to –0.16), *P* = .01
Early (≤72 hours) treatment failure, no. (%)[d]	40 (5.7)	45 (6.4)	OR 0.84 (0.53 to 1.34), *P* = .47
Late (>72 hours) treatment failure, no. (%)[d]	67 (9.5)	66 (9.3)	OR 0.97 (0.67 to 1.40), *P* = .86
Community-acquired pneumonia–related rehospitalization, no. (%)[e]	33 (5.0)	18 (2.7)	OR 1.85 (1.03 to 3.32), *P* = .04
Nosocomial infections, no. (%)	33 (4.4)	25 (3.3)	OR 1.31 (0.77 to 2.24), *P* = .32
Hyperglycaemia requiring insulin, no. (%)[f]	160 (22.1)	88 (12.0)	OR 2.15 (1.60 to 2.90), *P* < .001
Empyema/complicated parapneumonic effusion, no. (%)	12 (1.6)	14 (1.9)	OR 0.90 (0.41 to 1.96), *P* = .79
Gastrointestinal bleeding, no. (%)	5 (0.7)	5 (0.7)	OR 0.95 (0.27 to 3.33), *P* = .93
Neuropsychiatric complications, no. (%)	6 (0.8)	2 (0.3)	OR 2.98 (0.60 to 14.9), *P* = .18

Data are median (interquartile range) or n (%) unless otherwise stated.

Abbreviation: OR, odds ratio.

[a]Patients immediately admitted to an intensive care unit were excluded from this analysis (ie, analysis based on 1359 patients).

[b]Da

[c]Da

Recurrent pneumonia, other infection, pleuritic pain, adverse cardiovascular event, or diarrhea

[d]Data on early or on late treatment failure were not available from Fernandez-Serrano et al. and from Confalonieri et al. [8, 21] (ie, analysis based on 1411 patients).

[e]Data on community-acquired pneumonia–related rehospitalizations within 30 days of discharge were not available from Torres et al. [9] (ie, analysis based on 1386 patients).

[f]Data on hyperglycemia requiring insulin treatment were not available from Confalonieri et al. [8] (ie, analysis based on 1460 patients).

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Table 4. Subgroup Analyses for the Primary Outcome All-Cause Mortality at 30 days After Randomization Using Random Intercepts for Included Trials

Subgroup Variable	Corticosteroid (n = 748)	Placebo (n = 758)	Logistic Regression, Odds Ratio (95% Confidence Interval), *P* Value	*P* for Heterogeneity (Interaction)[a]
Pneumonia severity index[b]				.35
class I–III, no. (%)	3 (0.9)	2 (0.5)	1.70 (0.28–10.3), *P* = .56	
class IV and V, no. (%)	34 (8.4)	43 (11.6)	0.70 (0.44–1.13), *P* = .14	
Initial intensive care admission				.20
No, no. (%)	33 (4.9)	33 (4.9)	0.85 (0.50–1.45), *P* = .54	
Yes, no. (%)	4 (5.7)	12 (15.6)	0.34 (0.10–1.12), *P* = .08	
Initial median C-reactive protein				.72
< 188 mg/L, no. (%)	21 (5.8)	24 (6.4)	0.84 (0.44–1.61), *P* = .61	
≥ 188 mg/L, no. (%)	16 (4.3)	20 (5.5)	0.68 (0.32–1.43), *P* = .31	
Systemic inflammatory response system criteria				.08
0–1, no. (%)	11 (6.4)	7 (4.1)	1.70 (0.60–4.79), *P* = .31	
2 or more, no. (%)	22 (3.9)	33 (5.9)	0.59 (0.33–1.06), *P* = .08	
Antibiotic treatment before hospital admission				.23
No, no. (%)	25 (4.8)	26 (5.0)	0.93 (0.51–1.70), *P* = .83	
Yes, no. (%)	12 (5.3)	18 (7.7)	0.48 (0.21–1.10), *P* = .08	

[a]Logistic regression model including an interaction term of the respective subgroup variable with treatment group.

[b]The pneumonia severity index (PSI) is a clinical prediction rule to calculate the probability of morbidity and mortality among patients with community acquired pneumonia. PSI risk class I: aged ≤50 years and no risk factors; II: < 70; III: 71–90; IV: 91–130; V: >130 points.

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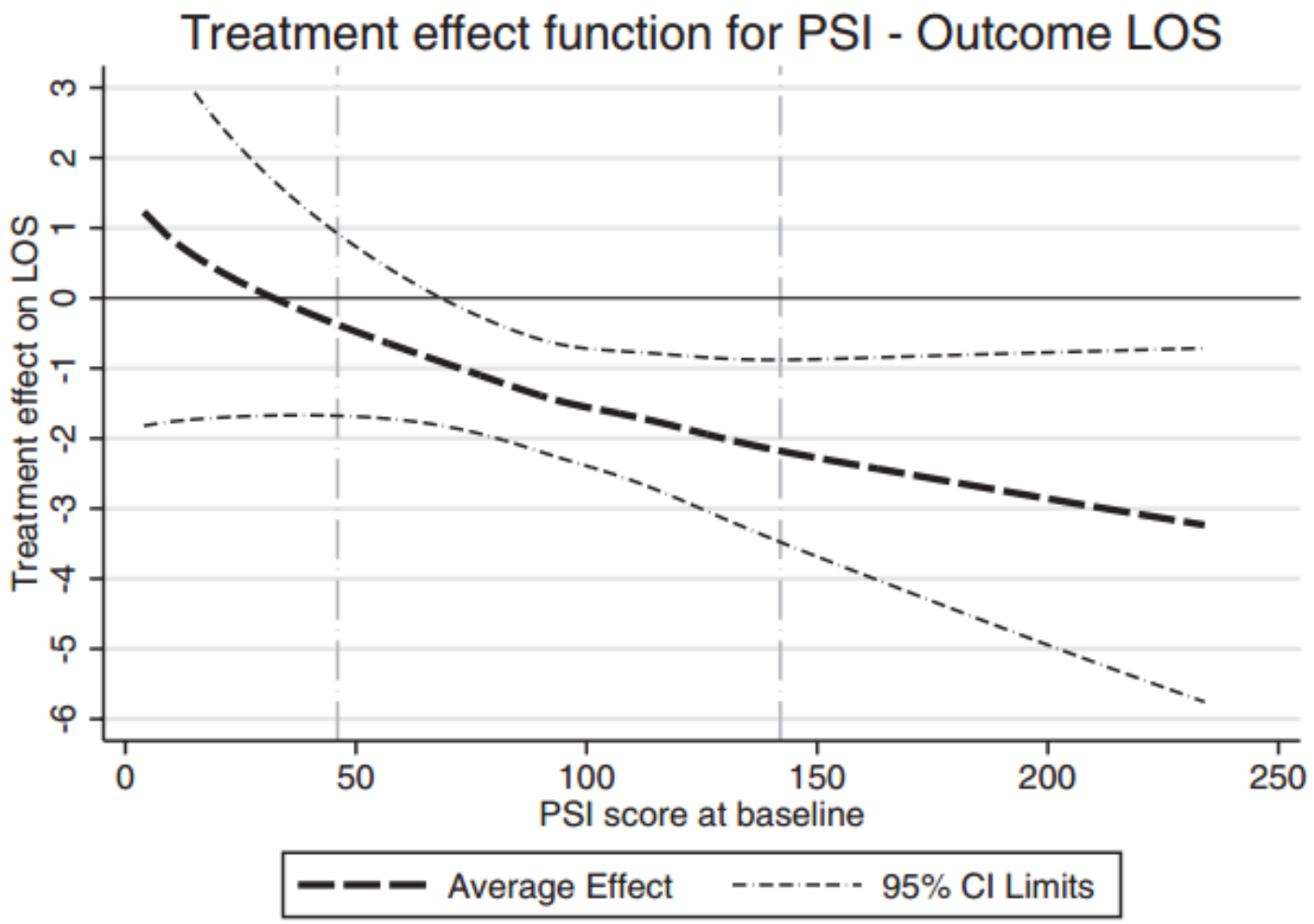


Figure 2. Multifractional polynomial interaction for pneumonia severity index score. Abbreviations: CI, confidence interval; LOS, length of stay; PSI, pneumonia severity index.

Clin Infect Dis. 2018 Jan 18;66(3):346-354

Online Supplement 12. Subgroup analyses for the secondary outcome CAP-RELATED RE-HOSPITALIZATION within 30 days after randomization*

Subgroup variables	Corticosteroid (n=748)	Placebo (n=758)	Logistic regression, OR (95%CI), p-value	p for heterogeneity (interaction) †
Pneumonia severity index‡				0·07
PSI class I-III – no. (%)	16 (5·1)	5 (1·4)	3·80 (1·38-10·5), p=0·01	
PSI class IV-V – no. (%)	17 (4·9)	13 (4·3)	1·15 (0·55-2·43), p=0·72	
Initial intensive care admission				-
No – no. (%)	32 (5·2)	18 (2·9)	1·80 (1·00-3·25), p=0·05	
Yes – no. (%)	1 (2·2)	0 (0·0)	-	
Initial median CRP				0·13
CRP< 188 mg/L – no. (%)	13 (3·8)	11 (3·1)	1·19 (0·52-2·70), p=0·68	
CRP≥ 188 mg/L – no. (%)	20 (6·4)	7 (2·3)	2·92 (1·21-7·02), p=0·02	
Systemic Inflammatory Response System criteria				0·18
0-1 – no. (%)	9 (5·6)	2 (1·3)	4·55 (0·97-21·5), p=0·055	
2 or more – no. (%)	23 (4·6)	16 (3·2)	1·45 (0·75-2·78), p=0·27	
Antibiotic treatment before hospital admission				0·27
No – no. (%)	21 (4·2)	14 (2·8)	1·50 (0·75-3·00), p=0·25	
Yes – no. (%)	12 (7·7)	4 (2·4)	3·42 (1·07-10·9), p=0·04	

* Values are given as median days (interquartile range), if not labeled otherwise.

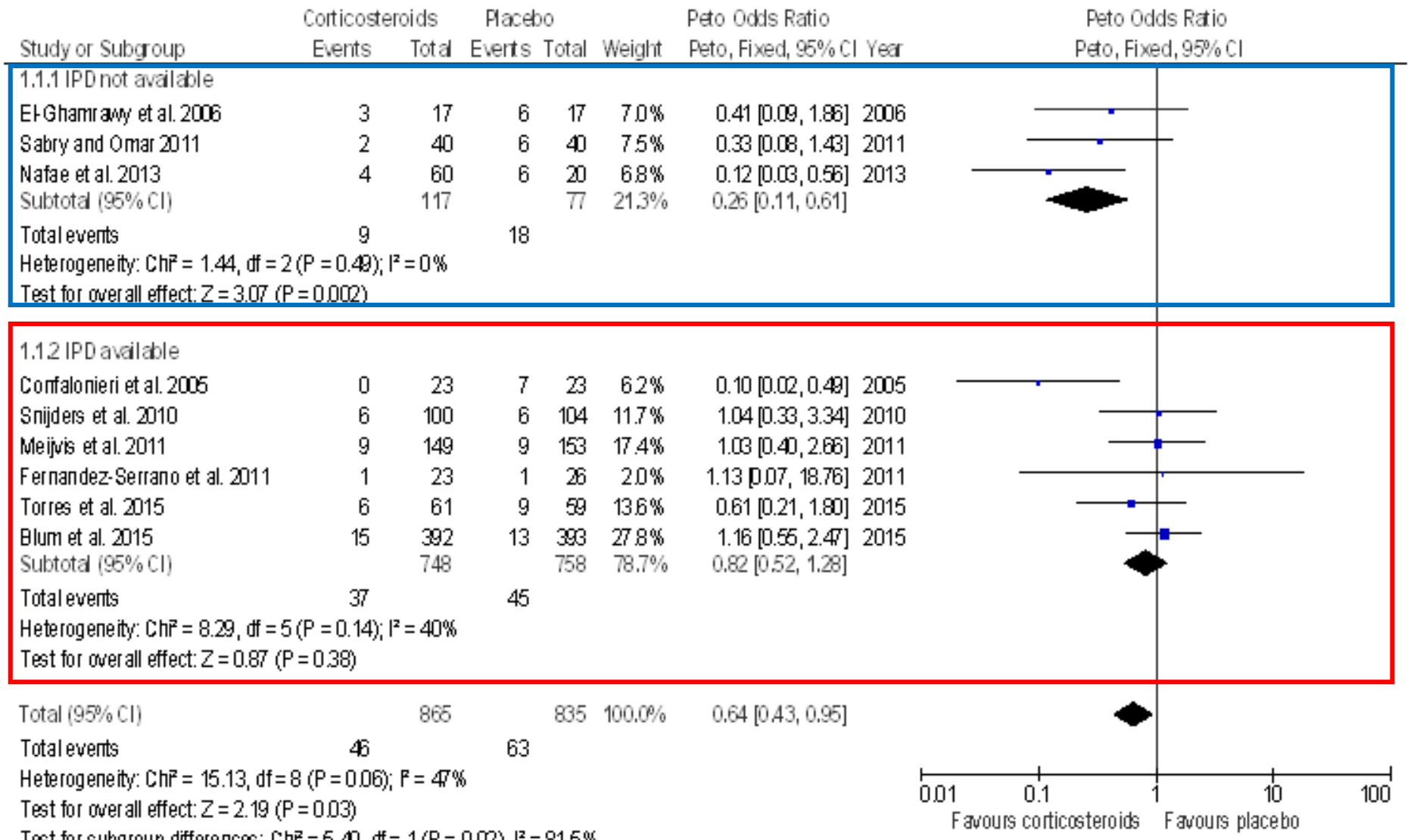
† Logistic regression model including an interaction term of the respective subgroup variable with treatment group

‡ The P eu ... morbidity and mortalit ... < 70, III: 71-90, IV: 91-130; V: > 130 points.

Abbreviations: CRP, C-reactive protein; CI, confidence interval

The difference in rehospitalizations was due predominantly to patients with nonsevere CAP

Online Supplement 18. Aggregate data meta-analysis for ALL-CAUSE MORTALITY at 30 days after randomization stratified by availability of individual patient data using Peto's method



- Adjunct corticosteroids for patients hospitalized with CAP
  - Reduce time to clinical stability
  - Reduce length of hospital stay by approximately 1 day (predominantly severe CAP)
  - Without a significant effect on overall mortality
  - But with an increased risk for CAP-related rehospitalization (predominantly non-severe CAP) and hyperglycemia.

NEJM Journal Watch

SUMMARY AND COMMENT | GENERAL MEDICINE, HOSPITAL MEDICINE

INFORMING PRACTICE

March 6, 2018

Steroids for Community-Acquired Pneumonia: The Body of Evidence Grows

Daniel D. Dressler, MD, MSc, SFHM, FACP reviewing Stern A et al. Cochrane Database Syst Rev 2017 Dec 13.

Two meta-analyses support systemic corticosteroids for hospitalized patients with CAP — especially severe CAP.

- Low dose (~40mg), short course (3-7days) systemic corticosteroids should be considered for hospitalized adults with severe CAP.

DT Eurich et al. BMJ 2017;356:j413

RESEARCH

OPEN ACCESS

Risk of heart failure after community acquired pneumonia: prospective controlled study with 10 years of follow-up

Dean T Eurich,[1,2] Thomas J Marrie,[3] Jasjeet K Minhas-Sandhu,[2] Sumit R Majumdar[1,2,4]

- Six hospitals and seven emergency departments in Edmonton, Alberta, Canada, 2000-02.
- Cohort study, prospectively recruited
- 4988 : CAP w/o history of HF
- 23060 : controls matched on age, sex, and setting of treatment (inpatient or outpatient) with up to five adults without pneumonia
- Outcome: Risk of hospital admission for HF up to 2012

DT Eurich et al. BMJ 2017;356:j413

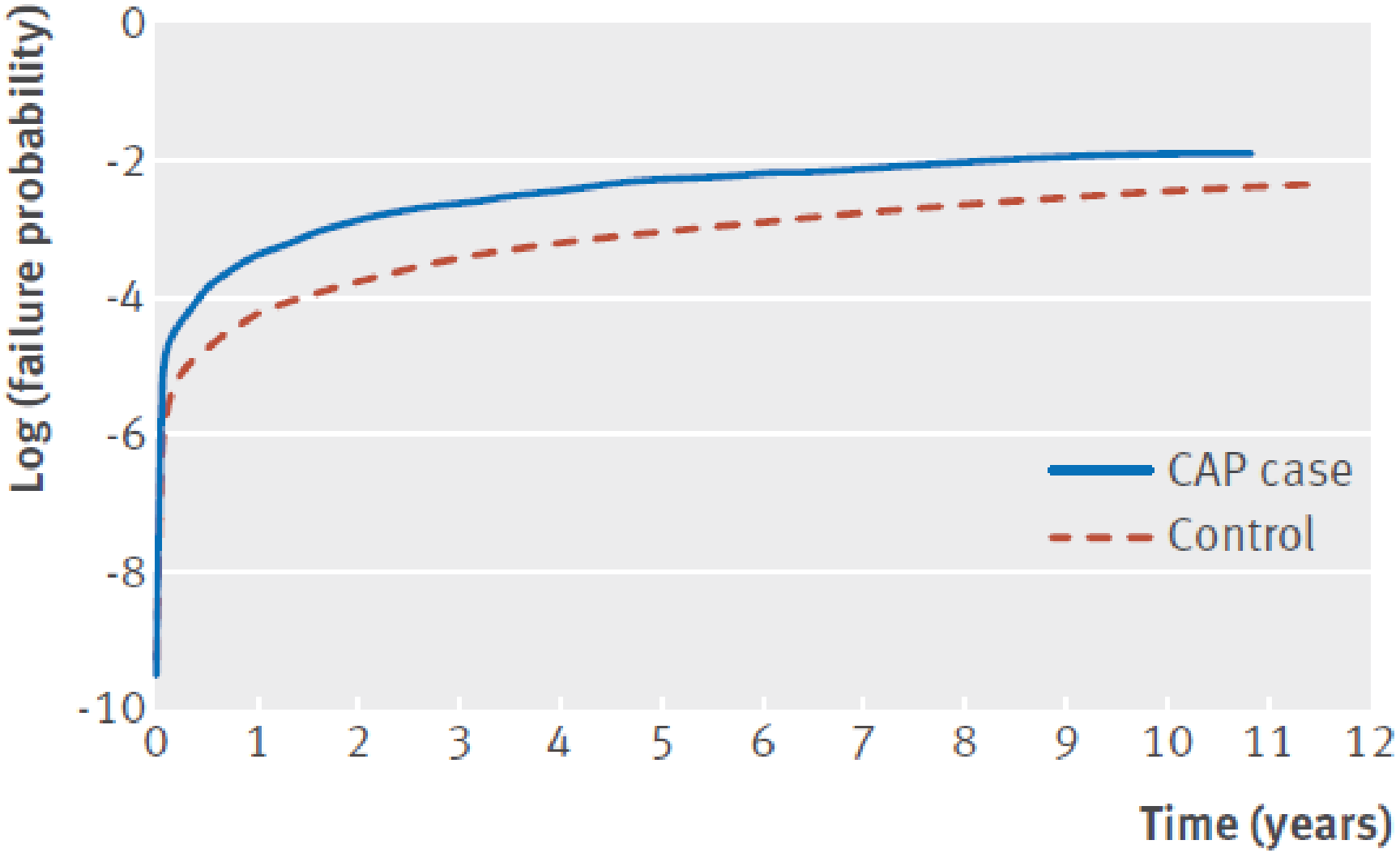


Fig 1 | Cumulative incidence of heart failure.
CAP=community acquired pneumonia

DT Eurich et al. BMJ 2017;356:j413

Table 2 | Risk of heart failure or heart failure and death among patients with community acquired pneumonia and controls. Values are numbers (percentages) unless stated otherwise

Analyses	Controls (n=23 060)	Patients with pneumonia (n=4988)	Adjusted hazard ratio (95% CI)	P value
Primary analysis				
Incident heart failure:				
Combined endpoint	1712 (7.4)	592 (11.9)	1.61 (1.44 to 1.81)	<0.001
Inpatients	875 (11.0)	334 (18.3)	1.94 (1.64 to 2.29)	<0.001
Outpatients	837 (5.6)	258 (8.2)	1.33 (1.12 to 1.57)	<0.001
Secondary analyses				
Incident heart failure within 90 days:				
Combined endpoint	145 (0.6)	68 (1.4)	1.52 (1.08 to 2.13)	<0.001
Inpatients	80 (1.0)	41 (2.3)	1.45 (0.90 to 2.34)	0.1
Outpatients	65 (0.4)	27 (0.9)	1.38 (0.79 to 2.39)	0.3
Incident heart failure within 1 year:				
Combined endpoint	321 (1.4)	164 (3.3)	1.86 (1.50 to 2.32)	<0.001
Inpatients	181 (2.3)	106 (5.8)	1.96 (1.46 to 2.64)	<0.001
Outpatients	140 (0.9)	58 (1.8)	1.54 (1.08 to 2.20)	0.019
Incident heart failure or all cause mortality:				
Combined endpoint	6041 (26.2)	2035 (40.8)	1.53 (1.44 to 1.63)	<0.001
Inpatients	3172 (39.8)	1178 (64.5)	1.77 (1.62 to 1.93)	<0.001
Outpatients	2869 (19.0)	857 (27.1)	1.34 (1.23 to 1.47)	<0.001

DT Eurich et al. BMJ 2017;356:j413

Supplemental Table 1 – Risk of Heart Failure Among Cases and Controls Stratified by Age

N=28 048	Control	Case	Adjusted Hazard Ratio with 95% Confidence interval	p-value
≤ 65 years (n, %)	**n=15838**	**n=3226**		
Incident HF Overall Follow-up				
Combined	347 (2.2)	155 (4.8)	1.98 (1.55 to 2.53)	<0.001
Inpatients	126 (3.1)	75 (8.9)	3.6 (2.29 to 5.7)	<0.001
Outpatients	221 (1.9)	80 (3.4)	1.46 (1.05 to 2.0)	0.02
>65 years (n, %)	**n=7222**	**n=1762**		
Incident HF Overall Follow-up				
Combined	1365 (18.9)	437 (24.8)	1.55 (1.36 to 1.77)	<0.001
Inpatients	749 (19.0)	259 (26.3)	1.77 (1.47 to 2.1)	<0.001
Outpatients	616 (18.7)	178 (22.9)	1.31 (1.07 to 1.60)	0.01

DT Eurich et al. BMJ 2017;356:j413

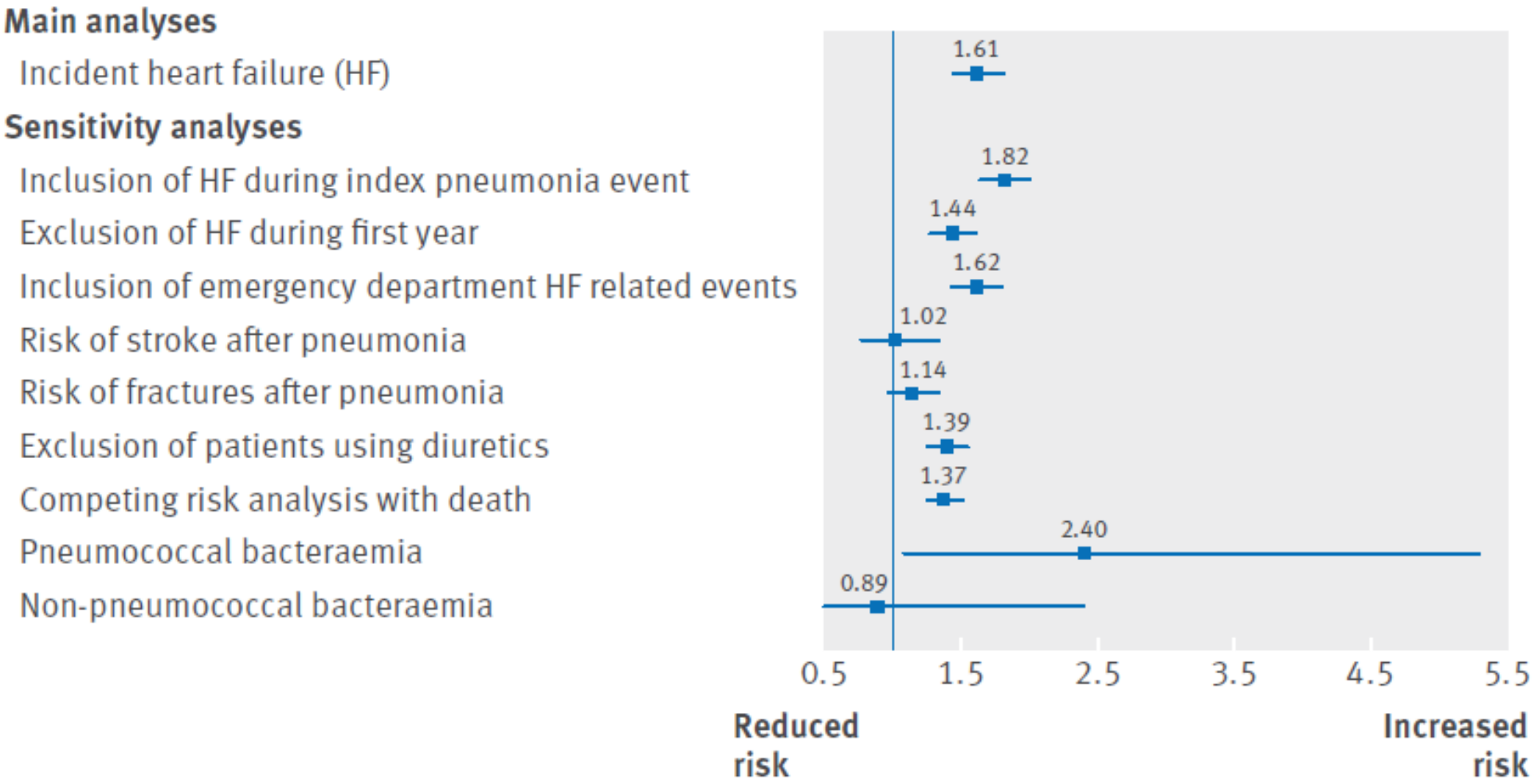


Fig 2 | Adjusted hazard ratios for incident heart failure in patients with community acquired pneumonia compared with controls

- Pneumonia increases systematic oxidative stress and inflammatory markers (eg, circulatory cytokines)
- → Increased risk of thrombogenesis, destabilization of atherosclerotic plaques, and endothelial dysfunction
- → Increased rates of ischaemic heart disease, atrial fibrillation, and reduced ventricular function

- **Even in those with young adults, less severe pneumonia**
- **Over the long term**

HAP/VAP

Kalil et al. Clin Infect Dis 2016; 63: e61–e111

Clinical Infectious Diseases Advance Access published July 14, 2016

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

[1]Department of Internal Medicine, Division of Infectious Diseases, University of Nebraska Medical Center, Omaha; [2]Division of Pulmonary and Critical Care Medicine, University of Connecticut School of Medicine, Farmington; [3]Brigham and Women's Hospital and Harvard Medical School, and [4]Harvard Pilgrim Health Care Institute, Boston, Massachusetts; [5]Department of Medicine, Critical Care Program, Queens University, Kingston, Ontario, Canada; [6]Division of Pulmonary, Critical Care and Sleep Medicine, University of California, San Diego; [7]Department of Medicine, Division of Pulmonary Critical Care and Sleep Medicine, State University of New York at Stony Brook; [8]Department of Surgery, Division of Trauma, Critical Care and Emergency Surgery, University of Michigan, Ann Arbor; [9]Department of Critical Care Medicine, National Institutes of Health, Bethesda, and [10]Johns Hopkins University School of Medicine, Baltimore, Maryland; [11]Department of Infectious Diseases, Hospital Universitari de Bellvitge, Bellvitge Biomedical Research Institute, Spanish Network for Research in Infectious Diseases, University of Barcelona, Spain; [12]Department of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, University at Buffalo, Veterans Affairs Western New York Healthcare System, New York; [13]Thoraxzentrum Ruhrgebiet, Department of Respiratory and Infectious Diseases, EVK Herne and Augusta-Kranken-Anstalt Bochum, Germany; [14]Department of Pathology and Microbiology, University of Nebraska Medical Center, Omaha; [15]Summa Health System, Akron, Ohio; [16]Department of Medicine, Division of Pulmonary and Critical Care Medicine, South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio; [17]Burns, Trauma and Critical Care Research Centre, The University of Queensland, [18]Royal Brisbane and Women's Hospital, Queensland, and [19]School of Medicine and Pharmacology, University of Western Australia, Perth, Australia; [20]Library and Knowledge Services, National Jewish Health, Denver, Colorado; and [21]Department of Clinical Epidemiology and Biostatistics and Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Torres et al. Eur Respir J 2017; 50: 1700582

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

Antoni Torres[1,16], Michael S. Niederman[2,16], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

Changes from previous guidelines

- HCAP excluded
- Early vs late onset → **MDR risk** high vs low, **mortality risk** high vs low
- Microbiological methods to diagnose
- Emphasis on use of **local antibiograms**
- 2 empirical antipseudomonal agents for only high risk pts
- Duration of treatment : **7-8 days**

Antimicrob Agents Chemother. 2014;58:5262-8

HCAP excluded

- HCAP are **not** at **high risk for MDR** pathogens
- Underlying patient characteristics are also important independent determinants of risk for MDR pathogens
- Recommendations regarding MDROs should be based on **validated risk factors** and not just healthcare exposure

Torres et al. Eur Respir J 2017; 50: 1700582

Early vs late onset → MDR high vs low risk

TABLE 2 Relationship between the frequency of multidrug-resistant (MDR) pathogens in early-onset nosocomial pneumonia (EOP)[#] *versus* the overall frequency of MDR pathogens causing hospital-acquired pneumonia (HAP)

First author [ref.]	MDR in EOP %	MDR in HAP overall %
Montravers [49]	Similar to overall	34
Leroy [50]	19	30
Ferrer [19]		26
Perbet [51]		Similar to overall
Restrepo [20]	27.8	30
Martin-Loeches [18]	51	57
Arvanitis [52]	10	25
Verhamme [53]	52	

[#]: EOP was defined as occurring ⩽5 days after admission.

Risk factor of MDR

- ATS:

Table 2. Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90 d

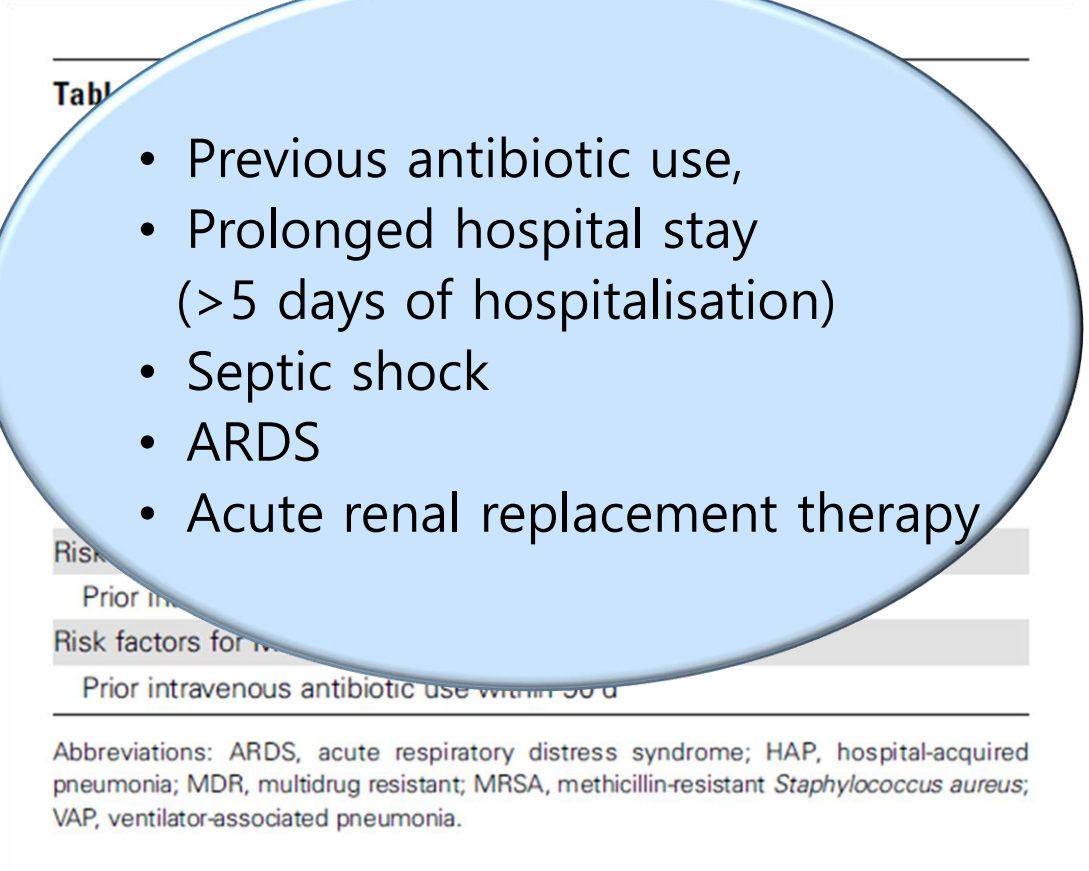
Abbreviations: ARDS, acute respiratory distress syndrome; HAP, hospital-acquired pneumonia; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

- ERS:
  - Previous antibiotic use,
  - Recent prolonged hospital stay (>5 days of hospitalisation)
  - Hospital settings with high rates (>25%) of MDR pathogens,
  - Previous MDR colonization

Risk factor of MDR

- ATS:

- Previous antibiotic use,
- Prolonged hospital stay
  (>5 days of hospitalisation)
- Septic shock
- ARDS
- Acute renal replacement therapy



Abbreviations: ARDS, acute respiratory distress syndrome; HAP, hospital-acquired pneumonia; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

- ERS:

- Previous antibiotic use,
- Recent prolonged hospital stay (>5 days of hospitalisation)
- Hospital settings with high rates (>25%) of MDR pathogens,
- Previous MDR colonization

Microbiological methods to diagnose

Invasive Sampling

Bronchoscopic techniques or mini-BAL:

- Bronchoalveolar lavage (BAL) **$>10^4$ CFU/mL**
- Protected specimen brush (PSB) **$>10^3$ CFU/mL**
- Blind bronchial sampling (mini-BAL) $>10^4$ CFU/mL

Non-invasive Sampling

- Endotracheal aspiration

Semiquantitative

- Presence or absence of pathogenic germs in culture
- Described growth as light, moderate or heavy
- Requires no specialized microbiologic methods

▶ CULTURE RESULT ◀

Organism #1 : Acinetobacter baumannii complex

Colony count : Heavily

Ampicillin/Sulbactam	R >= 32
Ticarcillin/CA	R >= 128
Piperacillin	R >= 128
Piperacillin/Tazobac	R >= 128
Cefotaxime	R >= 64
Ceftazidime	R >= 64
Cefepime	R >= 64
Aztreonam	R >= 64
Imipenem	R >= 16
Meropenem	R >= 16
Gentamicin	R >= 16
Ciprofloxacin	R >= 4
Minocycline	S 2
Tigecycline	S 2
colistin	S <= 0.5
Trimethoprim/Sulfa	R >= 320

Quantitative

- Threshold count of bacterial growth to differentiate between infection vs. colonization of lower airways.

▶ CULTURE RESULT ◀

Organism #1 : Acinetobacter baumannii complex

Colony count : >100,000 CFU/mL

Ampicillin/Sulbactam	R >= 32
Ticarcillin/CA	R >= 128
Piperacillin	R >= 128
Piperacillin/Tazobac	R >= 128
Cefotaxime	R >= 64
Ceftazidime	R >= 64
Cefepime	R >= 64
Aztreonam	R >= 64
Imipenem	R >= 16
Meropenem	R >= 16
Gentamicin	R >= 16
Ciprofloxacin	R >= 4
Minocycline	S 2
Tigecycline	S 2
colistin	S <= 0.5
Trimethoprim/Sulfa	R >= 320

Microbiological methods to diagnose

- ATS: non invasive sampling with semiquantative culture (weak,low)
  - Invasive quantative cultures -> below the diagnostic threshold for VAP -> antibiotics be withheld rather than continued (weak, low)
- ERS: distal quantative or proximal quantative or qualative culture (strong, low)
  - More antibiotic-free days in the invasive sampling group (5.0 days vs 2.2 days; P < .001) (Fagon et al. Ann Intern Med. 2000;132:621-630)

Treatment

- 2 empirical antipseudomonal agents for only **high risk** pts
  - ATS:

High risk of **mortality**
- Ventilator support
- Septic shock

High risk of **MDR**
- Previous antibiotic use,
- Prolonged hospital stay (>5 days of hospitalisation)
- Septic shock
- ARDS
- Acute RRT

  - ERS:

High risk of **mortality**
- Septic shock

High risk of **MDR**
- Previous antibiotic use,
- Recent prolonged hospital stay (>5 days of hospitalisation)
- Hospital settings with high rates (>25%) of MDR pathogens,
- Previous MDR colonization

- ATS

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus:	Plus:
	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

Abbreviations: HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*.

[a] Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock.

[b] Indications for MRSA coverage include intravenous antibiotic treatment during the prior 90 days, and treatment in a unit where the prevalence of MRSA among *S. aureus* isolates is not known or is >20%. Prior detection of MRSA by culture or non-culture screening may also increase the risk of MRSA. The 20% threshold was chosen to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use; hence, individual units can elect to adjust the threshold in accordance with local values and preferences. If MRSA coverage is omitted, the antibiotic regimen should include coverage for MSSA.

[c] If patient has factors increasing the likelihood of gram-negative infection, 2 antipseudomonal agents are recommended. If patient has structural lung disease increasing the risk of gram-negative infection (ie, bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended. A high-quality Gram stain from a respiratory specimen with numerous and predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non-glucose-fermenting microorganisms.

[d] Extended infusions may be appropriate.

[e] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another β-lactam–based agent because it has different targets within the bacterial cell wall [137].

Kalil et al. Clin Infect Dis 2016; 63: e61–e111

- ATS

High risk of **mortality**:
- Ventilator support,
- Septic shock

MRSA risk:
- IV anti within 90days,
- >20% of S.aureus,
- Previous detection of MRSA

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

High risk x MRSA risk x	**High risk x MRSA risk o**	**High risk o MRSA risk o**
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR		
Pipera-tazo Cefepime Levofloxacin Imi/meropenem	Piper-tazo Cefepime /ceftazidime Levo/ciprofloxacin Imi/meropenem aztreonam	2 antipseudomonal (avoid 2 b-lactams) Piper-tazo Cefepime /ceftazidime Levo/ciprofloxacin Imi/meropenem Amikacin/gentamicin/tobramycin aztreonam
MSSA cover	OR	
	Linezolid 600 mg	
	+	+
	Vancomycin linezolid	Vancomycin linezolid

Abbreviations: HAP, hospital-acquired pneumonia; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, meth…tive *Staphylococcus aureus*.

[a] Risk factors for mortality include need for ventilatory support due to pneumonia and septic shock.

[b] Indications for MRSA coverage include intravenous antibiotic treatment during the prior 90 days, and treatment in a u…reus isolates is not known or is >20%. Prior detection of MRSA by culture or non-culture screening may also increase the risk of MRSA. The 20…r effective initial antibiotic therapy against the risks of excessive antibiotic use; hence, individual units can elect to adjust the threshold in accorda…A coverage is omitted, the antibiotic regimen should include coverage for MSSA.

[c] If patient has factors increasing the likelihood of gram-negative infection, 2 antipseudomonal agents are recomm… negative infection (ie, bronchiectasis or cystic fibrosis), 2 antipseudomonal agents are recommended. A high-… predominant gram-negative bacilli provides further support for the diagnosis of a gram-negative pneumonia, including fermenting and non-glucose-fermenting micro…

[d] Extended infusions may be appropriate.

[e] In the absence of other options, it is acceptable to use aztreonam as an adjunctive agent with another βlactam–based agent because it has different targets within the…

High risk MDR:
- Previous antibiotic use,
- >5 days of hospitalisation
- Septic shock
- ARDS
- Acute RRT

- >10% G(-) are resistant to monotherapy
- Increasing the likelihood of **G(-)** infection :Structural lung disease

Pseudomonas:
- **Not high risk, dst known -> monotherapy**
- **High risk -> combination**
- **Aminoglycoside mono-> x**

Kalil et al. Clin Infect Dis 2016; 63: e61–e111

Strong, low-very low

- ATS

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Choose one gram-positive option from column A, one gram-negative option from column B, and one gram-negative option from column C. Note that the initial doses suggested in this table may need to be modified for patients with hepatic or renal dysfunction.

Abbreviations: CrCl, creatinine clearance; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a] Drug levels and adjustment of doses and/or intervals required.

[b] Extended infusions may be appropriate. Please see section XIII on pharmacokinetic/pharmacodynamic optimization of antibiotic therapy.

[c] On meta-analysis, aminoglycoside regimens were associated with lower clinical response rates with no differences in mortality.

[d] The dose may need to be lowered in patients weighing <70 kg to prevent seizures.

Cefepime IV: 2 g every 8 hours	Cefepime IV: 1-2 g every 8-12 hours
Gentamicin and tobramycin IV: 5-7 mg/kg/day	Gentamicin and tobramycin IV: 7 mg/kg/day
Amikacin IV: 15-20 mg/kg/day	Amikacin IV: 20 mg/kg/day

Torres et al. Eur Respir J 2017; 50: 1700582

- ERS

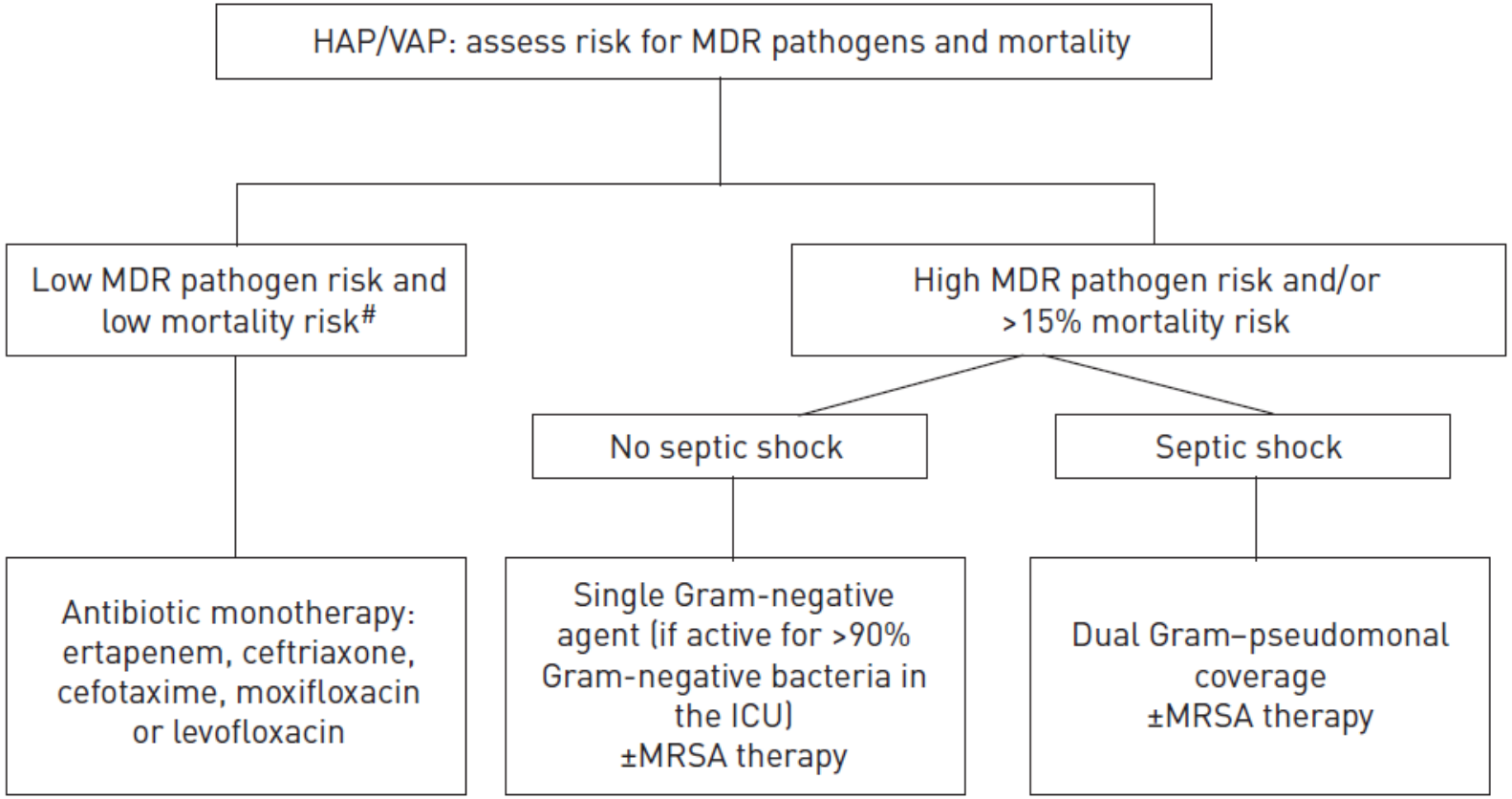
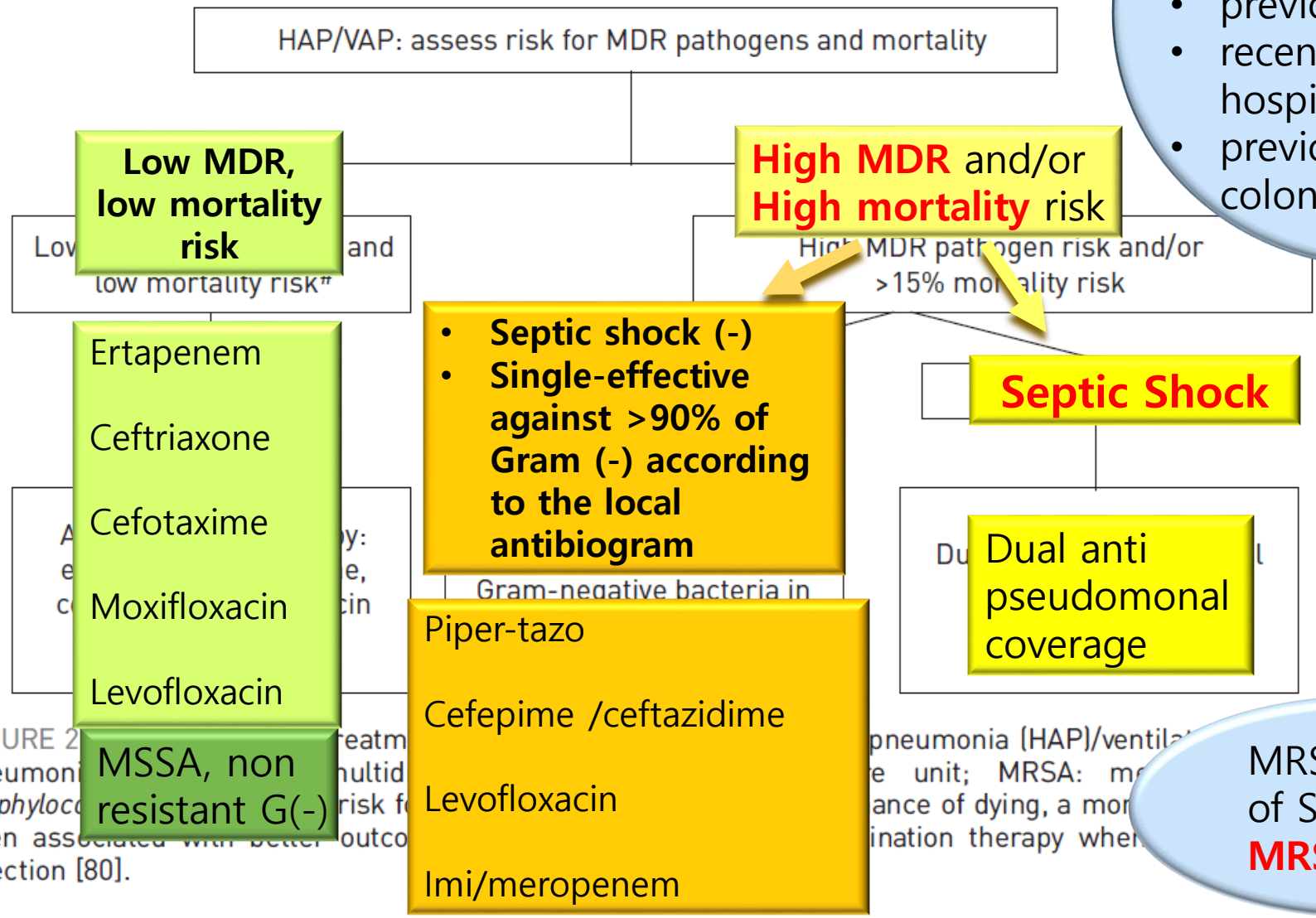


FIGURE 2 Empiric antibiotic treatment algorithm for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP). MDR: multidrug-resistant; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*. #: low risk for mortality is defined as a ⩽15% chance of dying, a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection [80].

Torres et al. Eur Respir J 2017; 50: 1700582

- ERS



High MDR risk
- high rates (>25%) of MDR pathogens setting
- previous antibiotic use,
- recent >5 days of hospitalisation
- previous MDR colonization

Weak, very low

Strong, low

MRSA ICU >25% of S.aureus, → **MRSA** coverage

Treatment: HAP/VAP caused by CRAB

- ATS:
  - IV polymyxin (**colistin** or polymyxin B) (strong, low)
  - Adjunctive **inhaled colistin** (weak, low)
  - **No** adjuctive **rifampin** (weak, moderate)
  - **No tigecycline** (strong, low)

Treatment: de-escalation

- ATS:
  - Suggest **de-escalated** rather than fixed (weak, low)

- ERS:
  - If initial combination therapy is started,
    - Continuing with a single agent based on culture results
    - Only consider maintaining definitive combination treatment based on sensitivities in patients with extensively drug-resistant (weak, low)

Treatment: others

- ATS:
  - Guided by Local Antibiotic-Resistance Data
  - VAT, we suggest not providing antibiotic therapy (weak, low)
  - Antibiotic dosing be determined using PK/PD data, rather than the manufacturer’s prescribing information (weak, low)

Treatment: duration

- ATS:
  - **7-day** (strong, moderate)
- ERS:
  - **7–8-day** course (Weak , moderate)
    - Also includes patients with nonfermenting Gram-negatives, Acinetobacter spp. and MRSA with a good response

TABLE 3 Patients in whom short duration of therapy may not be possible and in whom duration of therapy should be individualised

Initially inappropriate antibiotic therapy
Severely immunocompromised patients (such as neutropenia or stem cell transplant)
Highly antibiotic-resistant pathogens:
Pseudomonas aeruginosa
Carbapenem-resistant *Acinetobacter* spp.
Carbapenem-resistant *Enterobacteriaceae*
Second-line antibiotic therapy (*e.g.* colistin, tigecycline)

cystic fibrosis, empyema, lung abscess, cavitation or necrotizing pneumonia

Treatment: discontinuation

- ATS: **PCT** levels plus clinical criteria > clinical criteria alone (weak,low)
  - (It is not known if the benefits of using PCT levels to determine whether or not to discontinue antibiotic therapy exist in settings where standard antimicrobial therapy for VAP is already 7 days or less)
- ERS: do not recommend the routine PCT measurement
  - When the anticipated duration is 7–8 days. (strong, moderate)

Use of biomarkers

- ATS: 진단
  - PCT, sTREM-1 + Clinical Criteria < **Clinical Criteria alone** (weak, low)
  - CRP, CPIS + Clinical Criteria < Clinical Criteria alone (strong, moderate)

- ERS: 치료 반응
  - **Bedside clinical assessment** [체온, 가래양, purulence, CXR, WBC, PaO_2/FIO_2, CPIS, ODIN, SOFA, SAPS II and APACHE II]> CRP, PCT, copeptin, MR-proANP (Strong, moderate)

Take home message

- CAP:
  - 치료기간-최소 5일 &임상적 안정 보일 때 까지
  - Steroid: controversy가 있으나 일부 severe CAP에서 benefit
  - Risk of HF: non severe/young patients에도 long term하게 영향

- HAP/VAP
  - MDR/mortality risk에 따라 empirical therapy에 차이, risk가 있는 경우에만 double coverage
  - Local antibiogram을 참고, sensitivity에 따라 anti 조정
  - 치료 기간은 7-8일
  - Biomarker보다는 임상적 판단이 중요

감사합니다.