Supplementary Online Content

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This supplementary material was provided by the authors to give readers additional information about their work.

eMethods

Definitions

Definite bacterial VAP was defined as a positive pleural fluid culture and/or rapid cavitation of the lung infiltrate as determined by computed tomography and/or biopsy or autopsy specimen showing histological evidence of pneumonia (consolidation with large numbers of neutrophils in the bronchioles and adjacent alveoli in several adjacent low-power fields with or without tissue necrosis)[1]. Probable bacterial VAP was defined as a modified CPIS ≥5 combined with BAL cultures $>10^4$ cfu/mL for at least one organism or protected telescopic catheter $>10^3$ cfu/mL for at least one organism or endotracheal aspirate $>10^5$ cfu/mL for at least one organism. Possible VAP was defined as absence of the above-listed criteria with a modified CPIS ≥5.

Empirical therapy was considered adequate if the organism(s) identified in the enrolment specimen from a patient with probable VAP was susceptible in vitro to at least one of the antibiotics. The chief investigator reviewed all culture and susceptibility test results to determine the adequacy of empirical therapy.

ARDS was defined according to American-European consensus conference criteria[2]. Septic shock was defined as sepsis with systolic blood pressure <90 mmHg and/or mean arterial pressure <60 mmHg and/or systolic arterial pressure decrease >40 mmHg despite adequate fluid therapy, requiring vasopressor administration[3]. The presence of ARDS and/or septic shock was assessed daily from inclusion to day 28.

Antibiotics

Antibiotics were given according to local standard protocols. However, antibiotic therapy for at least 8 to 10 days was recommended except in patients with infection due to

nonfermenting gram-negative bacilli and/or in immunocompromised patients, in whom a duration of 15 days was recommended[4, 5]. Combination antibiotic treatment was recommended while waiting for the bacteriological results. A total combination therapy duration of 5 to 7 days was recommended in patients with multiresistant bacteria and/or *Pseudomonas aeruginosa*. Aminoglycosides were preferred over fluoroquinolones. Only bacterial VAP episodes were considered for the analysis. The decision to treat other pathogens found in the cultures was left to the ICU physicians.

eTable 1. Factors Influencing the Risk of Ventilator-Associated Pneumonia

	Overall n=284	Simvastatin n=146	Placebo n=138	*P* value
Enteral nutrition in the past 15 days, n (%)	239 (84)	123 (84)	116 (84)	1.0
Subglottic secretion drainage, n (%)	42 (15)	21 (14)	21 (15)	0.84
Closed-suction system, n (%)	26 (9)	12 (8)	14 (10)	0.57
Renal replacement therapy, n (%)	226 (80)	118 (81)	108 (78)	0.59
Swan-Ganz catheter, n (%)	13 (5)	3 (2)	10 (7)	0.04
Intracranial pressure monitoring, n (%)	42 (15)	26 (18)	16 (12)	0.14
Nasogastric tube, n (%)	260 (91)	129 (88)	131 (95)	0.05
Strict dorsal decubitus <30°, n (%)	34 (12)	18 (12)	16 (12)	0.85
Sinusitis, n (%)	11 (4)	8 (5)	3 (2)	0.15
Sedation, n (%)	215 (76)	108 (74)	107 (77)	0.48
Neuromuscular blocking agents, n (%)	78 (27)	41 (28)	37 (27)	0.81
H2-receptor antagonists, n (%)	21 (7)	15 (10)	6 (4)	0.06
Sucralfate, n (%)	1 (1)	0	1 (1)	0.49
Proton pump inhibitors, n (%)	221 (78)	112 (77)	109 (79)	0.65
Antacids, n (%)	27 (9)	14 (10)	13 (9)	0.96
Selective digestive decontamination, n (%)	8 (3)	4 (3)	4 (3)	0.93
Intravenous antibiotic for decontamination, n (%)	5 (2)	1 (1)	4 (3)	0.16
Oral decontamination with antiseptic, n (%)	151 (53)	79 (54)	72 (52)	0.74
Serum glucose maintained between 4 and 6 mmol/L, n (%)	181 (64)	91 (62)	90 (65)	0.61
Blood transfusion of at least 50% of the blood compartment, n (%)	13 (5)	7 (5)	6 (4)	0.86
Intrahospital transport, n (%)	87 (31)	50 (34)	37 (27)	0.16

eTable 2. Diagnosis of Ventilator-Associated Pneumonia and Antibiotic Therapy

	Overall n=284	Simvastatin n=146	Placebo n=138	*P* value
Possible VAP, n (%)	73 (26)	40 (27)	33 (24)	0.50
Probable VAP, n (%)	211 (74)	106 (73)	105 (76)	
Diagnosis based on positive BAL, n (%)	76 (36)	41 (39)	35 (33)	0.52
Diagnosis based on positive PTC, n (%)	63 (30)	28 (26)	35 (33)	
Diagnosis based on positive EA, n (%)	72 (34)	37 (35)	35 (33)	
Positive blood culture within 48 h, n (%)	30 (11)	13 (9)	17 (12)	0.35
Adequacy of empirical antibiotic treatment,* n (%)	172 (81)	91 (86)	81 (77)	0.10
Combination antibiotic therapy, n (%)	185 (65)	93 (64)	92 (67)	0.60

VAP, ventilator-associated pneumonia; BAL, bronchoalveolar lavage; PTC, protected telescopic catheter; EA, endotracheal aspirates; *for patients with probable VAP

eTable 3. Pathogens Identified in the Specimens Collected at Enrollment From Patients With Probable Ventilator-Associated Pneumonia

	Overall n=211	Simvastatin n=106	Placebo n=105	*P* value
Gram-positive	79	39	40	0.86
Staphylococcus aureus	54	27	27	
Methicillin-resistant Staphylococcus aureus	12	10	2	
Streptococcus spp.	20	10	10	
Other gram positive bacteria	5	2	3	
Gram-negative	30 (11)	13 (9)	17 (12)	0.35
Hemophilus influenza	15	11	4	
Klebsiella spp.	24	14	10	
Enterobacter spp.	16	5	11	
Serratia spp.	7	3	4	
Pseudomonas aeruginosa	42	21	21	
Escherichia coli	21	10	11	
Acinetobacter spp.	4	2	2	
Morganella spp.	4	2	2	
Proteus spp.	11	5	6	
Stenotrophomonas maltophilia	8	2	6	
Other gram-negative bacteria	16	10	6	
Multidrug-resistant organisms, n of patients (%)	70 (25)	34 (23)	36 (26)	0.58
High-risk organisms, n of patients (%)	85 (30)	44 (30)	41 (30)	0.94
Viruses, n of patients (%)	14 (7)	4 (4)	10 (10)	0.09

Multidrug-resistant organisms were organisms resistant to two or more antibiotic classes; HIGH-risk organisms were *Pseudomonas* spp., methicillin-resistant *S. aureus*, *S. maltophilia, Acinetobacter* spp., and multidrug-resistant bacteria

eTable 4. Course of Organ Dysfunctions

Organ dysfunctions	Day 1		Day 3		Day 7		Day 14	
	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo	Simvastatin	Placebo
SOFA score	7 [5-9]	6 [5-8]	5 [3-8]	5 [3-7]	4 [3-7]	4 [2-6.25]	3 [2-5]	3 [2-5]
SOFA subscores								
respiratory	3 [2-3]	3 [2-3]	3 [2-3]	3 [2-3]	2 [2-3]	2 [1-3]	2 [1-3]	2 [1-3]
cardiovascular	1 [0-4]	1 [0-4]	0 [0-2.5]	0 [0-2.5]	0 [0-1]	0 [0-1]	0 [0-0]	0 [0-1]
renal	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
hepatic	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
coagulation	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]	0 [0-0]
central nervous system	1 [0-3]	1 [0-3]	1 [0-3]	0 [0-3]	0 [0-3]	0 [0-2]	0 [0-2]	0 [0-1.75]
CPIS	7 [6-8]	7 [6-8]	4 [3-5]	4 [3-5]	4 [2.25-5]	4 [2-5]	3 [2-4]	4 (2-5)
creatinine, µmoL/L	67 [50-99]	68 [51-86]	65 [49-100]	66 [47-90]	63 [49-97]	63 [49-88]	56 [41-85]	56 [43-74]

Median [IQR] ; SOFA, Sequential Organ Failure Assessment score; CPIS, Clinical Pulmonary Infection Score

eTable 5. Infections Within the First 28 Days After Enrollment

	Overall n=284	Simvastatin n=146	Placebo n=138	*P* value
At least one new nosocomial infection, n (%)	98 (34)	46 (31)	52 (38)	0.27
VAP relapse or superinfection, n (%)	70 (25)	34 (23)	36 (26)	0.58
Bacteremia, n (%)	22 (8)	9 (6)	13 (9)	0.31
Urinary tract infection, n (%)	14 (5)	7 (5)	7 (5)	0.92
Catheter-related infection, n (%)	20 (7)	7 (5)	13 (9)	0.13
Septic shock, n (%)	45 (16)	20 (14)	25 (18)	0.31

VAP, ventilator-associated pneumonia

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