

Supplementary Material

Title: Adherence to Antibiotic Guidelines in Acute Patients With Suspected Severe Pneumonia: A Cohort Study

Authors: Sanne Schjødt¹, Marianne Lisby^{1,2}, Lotte Ebdrup³, Marie Kristine Jessen^{1,4}

¹ Research Center for Emergency Medicine, Department of Clinical Medicine, Aarhus University and Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, J103, DK-8200 Aarhus N, Denmark

² Department of Emergency Medicine, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, J103, DK-8200 Aarhus N, Denmark

³ Department of Medicine, Randers Regional Hospital, Skovlyvej 15, DK-8930 Randers, Denmark

⁴ Department of Anesthesiology and Intensive Care, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, C319, DK-8200 Aarhus N, Denmark

Text S1: Standard Prescription Packages (SPP)

Standard Prescription Packages (SPP) are a bundle of predefined prescriptions with dosing regimes for a specific indication, i.e., specific symptoms (i.e., suspected pneumonia, urinary tract infection, etc.) or diagnoses. The SPPs for specific indications are decided for each region; in this study, the Central Denmark Region. For patients with pneumonia of unknown origin, the Central Denmark Region has developed 10 different standard prescription packages, as follows: mild pneumonia, mild pneumonia with suspected atypical bacteria, moderate-severe pneumonia, severe pneumonia, aspiration pneumonia, mild-moderate hospital-acquired pneumonia, severe hospital-acquired pneumonia, pseudomonas aeruginosa pneumonia (ciprofloxacin i.v.), pseudomonas aeruginosa pneumonia (ciprofloxacin oral), and ventilator-associated pneumonia. In this study, we have focused on the Standard Prescription Package (SPP) for severe pneumonia, abbreviated as SPP-SP. One of the criteria for having severe pneumonia is concomitant sepsis. In the Central Denmark Region, a general “SPP: Sepsis/Septic shock of unknown origin” does exist. Patients receiving that SPP are not included in this study. Moreover, patients with hospital-acquired pneumonia (HAP) and aspiration pneumonia were not included in this study, since there are separate SPPs for those indications.

Table S2. Sequential Organ Failure Assessment (SOFA) score

The Sequential organ failure assessment (SOFA) score is in the study defined in accordance with The Third Consensus Definitions for Sepsis and Septic Shock (Sepsis 3) [1] adapted from Vincent et al. [2] with units used in the Danish Emergency Department.

System	Score				
	0	1	2	3	4
Respiration ^a					
PaO ₂ /FIO ₂ , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³ /μL	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	< 20	20-32	33-101	102-204	> 204
Cardiovascular					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose) ^b	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^b	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^b
Central nervous system					
Glasgow Coma Scale score ^c	15	13-14	10-12	6-9	< 6
Renal ^d					
Creatinine, mg/dL (μmol/L)	< 110	110-170	171-299	300-440	> 440
Urine output, mL/d ^d				< 500	< 200

Abbreviations: FIO₂, fraction of inspired oxygen; MAP, mean arterial pressure; PaO₂, partial pressure of oxygen.

^a In this study severe hypoxia was considered as saturation < 92 % (0 liter/min) and/or PaO₂ < 8 kPa (0 liter/min), saturation < 95 % (≥ 2 liter/min) and/or PaO₂/FiO₂ < 300.

^b Catecholamine doses are given as μg/kg/min for at least 1 hour.

^c Glasgow Coma Scale scores range from 3–15; higher score indicates better neurological function.

^d Urine output was not routinely measured, why renal function was based only on creatinine. Baseline creatinine (defined as the lowest value minimum 5 days and maximum 90 days before the patient was admitted) was used to calculate the increase in creatinine from baseline.

Table S3. CURB-65 score

<p>The CURB-65 score, for mortality risk assessment in the hospital is in the study defined in accordance with the recommendations of the National Institute for Health and Care Excellence (NICE) [3] based on Lim WS et al. [4].</p> <p>The CURB-65 score is calculated by giving 1 point for each of the following prognostic features:</p> <ul style="list-style-type: none">• C: Confusion *• U: Raised blood urea nitrogen (over 7 mmol/liter)• R: Raised respiratory rate (30 breaths per minute or more)• B: Low blood pressure (diastolic 60 mmHg or less, or systolic less than 90 mmHg)• 65: Age 65 years or more <p>People are stratified for risk of death (within 30 days) as follows:</p> <p>0 or 1: low risk (less than 3% mortality risk)</p> <p>2: intermediate risk (3-15% mortality risk)</p> <p>3 to 5: high risk (more than 15% mortality risk)</p>
<p>(*) In our retrospective study, the parameter confusion was based on Glasgow Coma Scale (GCS) and the status of consciousness. GCS < 15 and/or any other status than habitual, the patient was considered confused.</p>

Table S4. Patient characteristics total and missings

Variable	Total (n = 270)	Missings n (%)
Age (years), median [IQR]	76 [65;83]	0 (0)
Gender, male, n (%)	156 (58)	0 (0)
COMORBIDITIES ^a , n (%)		
Diabetes ^b	61 (23)	
COPD ^c	77 (29)	
Severe COPD ^d	49 (64)	
Asthma ^e	55 (20)	
Chronic heart disease ^e	109 (40)	
Chronic liver disease ^f	16 (6)	
Chronic kidney disease ^g	28 (10)	
None mentioned above	65 (24)	
No patient journal available ^h	< 5 (< 2)	
VITAL SIGNS AT TRIAGE		
Oxygen treatment, n (%)	162 (60)	0 (0)
Nasal cannula	138 (85)	
High Nasal Flow	0 (0)	
NIV	< 5 (<2)	
Intubated	< 5 (<2)	
Other ⁱ	19 (12)	
Oxygen flow (L/min), median [IQR]	2 [0;4]	0 (0)
Oxygen saturation (%), median [IQR]	93 [91;96]	1 (0.4)
Respiratory rate (breaths/min), median [IQR]	24 [20;28]	2 (0.7)
Systolic blood pressure (mmHg), mean (SD)	134 (28)	0 (0)
Diastolic blood pressure (mmHg), median [IQR]	72 [61;83]	0 (0)
Mean arterial pressure (mmHg), mean (SD)	94 (21)	0 (0)
Heart rate (beats/min), mean (SD)	101 (22)	0 (0)
Temperature (°C), mean (SD)	38.0 (1.1)	5 (1.9)
GCS score, median [IQR]	15 [15;15] (full range: 3-15)	4 (1.5)
LABORATORY VALUES ^j , median [IQR]		
Bilirubin (μmol/L)	11 [7;16]	7 (2.6)
Creatinine (μmol/L)	83 [61;114]	1 (0.4)
Urea (mmol/L)	7.3 [5;10.5]	7 (2.6)
C-reactive protein (mg/L)	141 [58;261]	1 (0.4)
Leucocytes (x10 ⁹ /L)	12.5 [9.7;17.3]	1 (0.4)
Platelet count (x10 ⁹ /L)	255 [191;323]	8 (3)
Arterial blood gas performed ^j , n (%)	196 (73)	
Arterial blood gas PaO ₂ (kPa), median [IQR]	8.7 [7.6;9.8]	0 (0)
SCORING SYSTEMS		
Total SOFA score ^k , median [IQR]	2 [1;3]	
Total CURB-65 score ^k mean (SD)	2 (1)	
Confusion (C), n (%)	57 (21)	
Urea > 7 mmol/L (U), n (%)	137 (51)	
Respiration ≥ 30/min (R), n (%)	57 (21)	
Blood pressure (B), n (%)	62 (23)	
Systolic < 90 mmHg and/or diastolic ≤ 60 mmHg		
Age ≥ 65 (65), n (%)	203 (75)	
CURB-65 score 3-5, n (%)	82 (30)	

Abbreviations: COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; SPP, Standard Prescription Package; NIV, non-invasive ventilation; SPP-time, Physician prescription time of the SPP.

^a Comorbidities are based on medical history, ICD-10 codes, and medical treatment overview.

^b Diabetes type 1 or 2, medical treatment (oral or injection).

^c COPD and/or asthma requiring daily medicine.

^d Severe COPD is defined as FEV1 < 50 %, home oxygen treatment, and/or combined inhalation medicine compatible with severe COPD.

^e Chronic heart disease, including ischemic heart disease, cardiac arrest (earlier), chronic heart failure with/without preserved ejection fraction, atrial fibrillation/atrial flutter (paroxysmal, persistent, chronic), earlier myocardial infarction (ST or non-ST), unstable angina pectoris.

^f Chronic liver disease, including hepatitis, cirrhosis, steatosis, and steatohepatitis.

^g Chronic kidney disease stage 3A or worse (GFR < 60 mL/min/1.73 m²) or kidney transplant.

^h Patients from other regions, e.g., the Capital Region of Denmark, where the patient journal is not available.

ⁱ Hudson mask, venturi mask, mask unspecified.

^j Laboratory values in the emergency department where the patient was *admitted*. If several blood tests (or arterial blood gas), the test closest to SPP-time was chosen.

^k Based on vital signs at triage. SOFA score; see supplementary Table S2. CURB-65 score (C = Confusion, Urea > 7 mmol/L, Respiratory rate ≥ 30/min, Blood pressure (Diastolic ≤ 60 mmHg or systolic < 90 mmHg, age ≥ 65 years).

Table S5. (A) Imaging and (B) Microbiology

A

Variable	All patients treated with SPP-SP	Criteria for SPP-SP	Criteria for SPP-SP
	(n = 270)	fulfilled (n = 103)	not fulfilled (n = 167)
Chest X-ray performed ^a, n (%)	235 (87)	90 (87)	145 (87)
Before SPP-time	159 (68)	65 (72)	94 (65)
No new infiltrate	63 (27)	29 (32)	34 (23)
Presence of new infiltrate/infiltrates	172 (73)	61 (68)	111 (77)
Multiple lobes involved	102 (43)	46 (51)	56 (39)
Chronic infiltrate/infiltrates	56 (24)	24 (27)	32 (22)
Infiltrate basal/inferior lobe dxt ^b	79 (34)	27 (30)	52 (36)
Infiltrate basal/inferior lobe sin ^b	75 (32)	26 (29)	49 (34)
Infiltrate apical/superior lobe dxt ^b	41 (17)	20 (22)	21 (14)
Infiltrate apical/superior lobe sin ^b	34 (14)	16 (18)	18 (12)
Infiltrate middle lobe ^b	14 (6)	7 (8)	7 (5)
Diffuse infiltrate/infiltrates ^{b,c}	50 (21)	18 (20)	32 (22)
CT-Thorax performed ^{a,d}, n (%)	35 (13)	12 (12)	23 (14)
Before SPP-time	24 (69)	8 (67)	16 (70)
No new infiltrate	7 (20)	2 (17)	5 (22)
Presence of new infiltrate/infiltrates	28 (80)	10 (83)	18 (78)
Multiple lobes involved	26 (74)	9 (75)	17 (74)
Chronic infiltrate/infiltrates	8 (23)	4 (33)	4 (17)
Infiltrate basal/inferior lobe dxt ^b	16 (46)	5 (42)	11 (48)
Infiltrate basal/inferior lobe sin ^b	11 (31)	3 (25)	8 (35)
Infiltrate apical/superior lobe dxt ^b	13 (37)	3 (25)	10 (43)
Infiltrate apical/superior lobe sin ^b	7 (20)	2 (17)	5 (22)
Infiltrate middle lobe ^b	7 (20)	1 (8)	6 (26)
Diffuse infiltrate/infiltrates ^{b,c}	9 (26)	3 (25)	6 (26)
Ground-glass opacity ^b	17 (49)	5 (42)	12 (52)
Both chest X-ray and CT-Thorax ^a, n (%)	16 (6)	6 (6)	10 (43)

Abbreviations: SPP, Standard Prescription Package; SPP-time, physician prescription time of the SPP; dxt, dexter; sin, sinister; CT, computed tomography; CT-TAB, computed tomography of thorax, abdomen, and pelvis.

^a In the emergency department where the patient was *admitted*.

^b Relating to *new* infiltrate.

^c If X-ray description considered infiltrates “diffuse”, it may be unilateral or bilateral. Depending on the further description, it was decided whether multiple lobes were involved.

^d CT-Thorax *or* CT-Lung *or* CT-TAB.

B

Variable	All patients treated	Criteria for SPP-SP	Criteria for SPP-SP
	with SPP-SP	fulfilled	not fulfilled
	(n = 270)	(n = 103)	(n = 167)
Urine culture, n (positive)/ n(total)	34/110	17/47	17/63
Urine culture etiology	Table S6A	Table S6A	Table S6A
Blood culture, n (positive)/ n(total)	39/257	20/100	19/157
Blood culture etiology	Table S6B	Table S6B	Table S6B
Sputum culture, n (positive)/ n(total)	38/130	14/42	24/88
Sputum culture etiology	Table S6C	Table S6C	Table S6C
PCR (<i>Legionella pneumophila</i> + <i>Mycoplasma pneumonia</i>), n (positive)/ n(total)	< 5/99	0/35	< 5 /64
Other tests, n (positive)/ n(total)			
Influenza A and/or Influenza B	7/226	< 5/79	6/147
SARS-CoV-2	23/233	8/82	15/151
RS-virus	8/225	< 5/79	6/146

Abbreviations: RS-virus, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; SPP, Standard Prescription Package; SPP-time, physician prescription time of the SPP.

Table S6. (A) Urine culture, (B) blood culture and (C) sputum culture

A

Urine culture	Frequency, n	Proportion, %
Negative	76	69
Positive	34	31

Bacterial etiology, group	Frequency, n
Enterobacteriaceae	24
Non-Enterobacteriaceae	< 5
Others gram-negative	< 5
Gram-positive	12

The most frequent bacterial etiology in urine culture was *Escherichia coli*.

Enterobacteriaceae included: *Klebsiella oxytoca*, *Klebsiella pneumoniae* complex, *Klebsiella aerogenes*, *Enterobacter cloacae* complex, *Escherichia coli*, *Proteus mirabilis*, *Citrobacter koseri*, and *Citrobacter freundii* complex.

Non-Enterobacteriaceae included: *Pseudomonas aeruginosa*.

Gram-positive included: *Staphylococcus aureus*, *Coagulase-Negative staphylococci*, *Enterococcus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Aerococcus urinae*, and *Aerococcus sanguinicola*.

B

Blood culture	Frequency, n	Proportion, %
Negative	218	85
Positive	39	15

Bacterial etiology, group	Frequency, n
Enterobacteriaceae	8
Micrococcaceae	< 5
Others gram-negative	< 5
Gram-positive	31

The most frequent bacterial etiology in blood culture was *Streptococcus pneumoniae*.

Enterobacteriaceae included: *Klebsiella oxytoca*, *Enterobacter cloacae* complex, *Escherichia coli*, *Escherichia coli* ESBL (+), and *Serratia marcescens*.

Micrococcaceae included: *Micrococcus*.

Other gram-negative bacteria included: *Moraxella catarrhalis* and *Neisseria meningitidis*.

Gram-positive included: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Coagulase-Negative staphylococci*, *Streptococcus mitis* group, *Corynebacterium species*, *Enterococcus faecium*, *Streptococcus pyogenes*, and *Actinotignum (Actinobaculum schaalii)*.

C

Sputum culture	Frequency, n	Proportion, %
Negative	92	71
Positive	38	29

Bacterial etiology	Frequency, n
Enterobacterales	7
Non-Enterobacteriaceae	< 5
Others gram-negative	14
Gram-positive	19

The most frequent bacterial etiology in sputum culture was *Streptococcus pneumoniae*.

Enterobacteriaceae included: *Klebsiella oxytoca*, *Klebsiella pneumoniae* complex, *Enterobacter cloacae* complex, and *Serratia marcescens*.

Non-Enterobacteriaceae included: *Pseudomonas aeruginosa*.

Others gram-negative bacteria included: *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Stenotrophomonas maltophilia*.

Gram-positive included: *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pyogenes*.

References

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama*. 315(8):801-10. doi:10.1001/jama.2016.0287
2. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 22(7):707-10. doi:10.1007/bf01709751
3. National Institute for Health and Care Excellence: Guidelines. *Pneumonia in adults: diagnosis and management*. National Institute for Health and Care Excellence (NICE).
4. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. May 2003;58(5):377-82. doi:10.1136/thorax.58.5.377