

# Supplementary appendix

This appendix has been provided by the authors to provide additional information about their research.

This appendix is an on-line supplement to:

## **Clinical and economic outcomes attributable to carbapenem-resistant Enterobacterales and delayed appropriate antibiotic therapy in hospitalized patients**

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**Table S1** International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)  
codes of infections

<b>Diseases</b>	<b>References</b>	<b>ICD-10 codes</b>
Urinary tract infection (UTI)	Urinary tract infection, site not specified	N39.0
Pneumonia	Pneumonia due to <i>Klebsiella pneumoniae</i>	J15.0
	Pneumonia due to <i>Pseudomonas</i>	J15.1
	Pneumonia due to <i>Escherichia coli</i>	J15.5
	Pneumonia due to other Gram-negative bacteria	J15.6
	Bacterial pneumonia, unspecified	J15.9
	Lobar pneumonia, unspecified	J181
	Other pneumonia, organism unspecified	J188
	Pneumonia, unspecified	J189
Intra-abdominal infections (IAI)	Diverticulitis of small intestine with perforation and abscess.	K570
	Acute peritonitis	K650
	Other peritonitis.	K658
	Peritonitis, unspecified.	K659
	Idiopathic acute pancreatitis	K850
	Other acute pancreatitis	K858
	Acute pancreatitis, unspecified	K859
Blood stream infections (BSI)	Sepsis due to other Gram-negative organisms	A415
	Sepsis, unspecified (septicemia)	A419
	Bacterial infection, unspecified (Bacteremia NOS)	A499

**Table S2** Treatment Algorithm for Enterobacterales infections

Type of infection	Carbapenem-resistant Enterobacterales (CRE)		Carbapenem-susceptible Enterobacterales (CSE)	
	Core Drugs	Possible Adjunct Drugs	ESBL	Non-ESBL
Bloodstream infection	• Polymyxins	• Meropenem • Tigecycline • Fosfomycin	• Ertapenem OR meropenem OR imipenem-cilastatin	• Susceptible anti-gram-negative bacteria e.g., 3 <sup>rd</sup> cephalosporins, fluoroquinolones, aminoglycosides, and BLBIs
Pneumonia	• Polymyxins	• Meropenem	• Ertapenem OR meropenem OR imipenem-cilastatin	• Susceptible anti-gram-negative bacteria e.g., 3 <sup>rd</sup> cephalosporins, fluoroquinolones, aminoglycosides, and BLBIs
Urinary tract infection	• Polymyxins	• Meropenem • Tigecycline • Fosfomycin	• Ertapenem OR meropenem OR imipenem-cilastatin • Aminoglycosides • Piperacillin/Tazobactam	• Susceptible anti-gram-negative bacteria e.g., 3 <sup>rd</sup> cephalosporins, fluoroquinolones, aminoglycosides, and BLBIs
Intra-abdominal infection	• Polymyxins	• Meropenem • Tigecycline • Fosfomycin	• Ertapenem OR meropenem OR imipenem-cilastatin • Tigecycline	• Susceptible anti-gram-negative bacteria e.g., 3 <sup>rd</sup> cephalosporins, fluoroquinolones, aminoglycosides, and BLBIs

**Abbreviation:** ESBL, Extended-Spectrum  $\beta$ -lactamase, BLBIs,  $\beta$ -lactamase -  $\beta$ -lactamase inhibitors

**Table S3** Distribution of antibiotic therapy in a comparison of patients with carbapenem-resistant Enterobacterales (CRE) and carbapenem-susceptible Enterobacterales (CSE) according to the receipt of appropriate or delayed appropriate antibiotic therapy

<b>Characteristics</b>	<b>All patients (n=4509)</b>	<b>CSE with AAT (n=3041)</b>	<b>CSE with Delayed AAT (n=841)</b>	<b>CRE with AAT (n=74)</b>	<b>CRE with Delayed AAT (n=553)</b>
3rd generation cephalosporins	2105 (46.68)	1589 (52.25)	396 (47.09)	0 (0.00)	120 (21.70)
Carbapenems	998 (22.13)	782 (25.72)	0 (0.00)	0 (0.00)	216 (39.06)
BLBIs	632 (14.02)	423 (13.91)	99 (11.77)	0 (0.00)	110 (19.89)
Fluoroquinolones	192 (4.26)	124 (4.08)	37 (4.40)	0 (0.00)	7 (1.27)
Aminoglycosides	24 (0.53)	14 (0.46)	5 (0.59)	0 (0.00)	5 (0.90)
Fosfomycin	41 (0.91)	26 (0.85)	10 (1.19)	5 (6.76)	0 (0.00)
Colistin	115 (0.55)	51 (1.68)	6 (0.71)	58 (78.38)	0 (0.00)
Carbapenems + Tigecycline	1 (0.02)	0 (0.00)	0 (0.00)	1 (1.35)	0 (0.00)
Carbapenems + Fosfomycin	27 (0.60)	17 (0.56)	0 (0.00)	10 (13.51)	0 (0.00)
3rd generation cephalosporins +Aminoglycosides	25 (0.55)	14 (0.46)	5 (0.59)	0 (0.00)	6 (1.08)
Not received any antibiotic therapy in the index date	336 (7.45)	0 (0.00)	279 (33.17)	0 (0.00)	57 (10.31)

**Abbreviations:** AAT, appropriate antibiotic therapy; BLBIs, Beta-lactam-beta-lactamase inhibitors; CRE, carbapenem-resistant Enterobacterales; CSE, carbapenem-susceptible Enterobacterales

**Table S4** Demographic and Clinical Characteristics of patients in a comparison of patients with carbapenem-resistant Enterobacterales (CRE) and carbapenem-susceptible Enterobacterales (CSE) according to the receipt of appropriate or delayed appropriate antibiotic therapy

<b>Characteristics</b>	<b>All patients (n=4509)</b>	<b>CSE with AAT (n=3041)</b>	<b>CSE with Delayed AAT (n=841)</b>	<b>CRE with AAT (n=74)</b>	<b>CRE with Delayed AAT (n=553)</b>	<b>P-value</b>
<b>Demographics Characteristics</b>						
Male	1952 (43.29)	1236 (40.64)	356 (42.33)	47 (63.51)	313 (56.60)	<0.001
Age, mean (SD)	65.21 (18.68)	65.74 (17.88)	63.69 (21.53)	62.90 (16.77)	64.89 (18.45)	0.025
Age ≥65 years	2595 (57.55)	1760 (57.88)	485 (57.67)	35 (47.30)	315 (56.96)	0.336
<b>Health insurance</b>						0.980
CSMBS	878 (19.47)	589 (19.37)	173 (20.57)	16 (21.62)	100 (18.08)	
SSS	177 (3.93)	120 (3.95)	32 (3.80)	2 (2.70)	23 (4.16)	
UCS	3418 (75.80)	2307 (75.86)	629 (74.79)	56 (75.68)	426 (77.03)	
Others	36 (0.80)	25 (0.82)	7 (0.83)	0 (0.00)	4 (0.72)	
<b>Ward</b>						<0.001
Medical ward	2741 (60.79)	1958 (64.39)	455 (54.10)	29 (39.19)	299 (54.07)	
Surgical ward	461 (10.22)	307 (10.10)	79 (9.39)	8 (10.81)	67 (12.12)	
ICU	706 (15.66)	429 (14.11)	111 (13.20)	37 (50.00)	129 (23.33)	
Others	601 (13.33)	347 (11.41)	196 (23.31)	0 (0.00)	58 (10.49)	
<b>Site of infection</b>						<0.001
BSI	764 (16.94)	599 (19.70)	102 (12.13)	6 (8.11)	57 (10.31)	
Pneumonia	1563 (34.66)	957 (31.47)	255 (30.32)	57 (77.03)	294 (53.16)	
UTI	2115 (46.91)	1447 (47.58)	470 (55.89)	8 (10.81)	190 (34.36)	
IAI	67 (1.49)	38 (1.25)	14 (1.66)	3 (4.05)	12 (2.17)	
<b>Length of hospital stay before infection</b>						

<b>Characteristics</b>	<b>All patients (n=4509)</b>	<b>CSE with AAT (n=3041)</b>	<b>CSE with Delayed AAT (n=841)</b>	<b>CRE with AAT (n=74)</b>	<b>CRE with Delayed AAT (n=553)</b>	<b>P-value</b>
Mean score (SD)	5.33 (10.87)	3.57 (7.80)	6.07 (13.27)	20.46 (16.24)	11.86 (15.39)	<0.001
Median (IQR)	1 (1-5)	1 (0-3)	1 (1-6)	15.5 (10-32)	7 (1-16)	<0.001
<b>Type of infection</b>						
Community-acquired infection	2872 (63.69)	2161 (71.06)	516 (61.36)	7 (9.46)	188 (34.00)	<0.001
Hospital-acquired infection	1637 (36.31)	880 (28.94)	325 (38.64)	67 (90.54)	365 (66.00)	
<b>Comorbidities</b>						
Myocardial infarction	193 (4.28)	138 (4.54)	41 (4.88)	3 (4.05)	11 (1.99)	0.021
Congestive heart failure	378 (8.38)	254 (8.35)	79 (9.39)	4 (5.41)	41 (7.41)	0.492
Peripheral vascular disease	29 (0.64)	13 (0.43)	5 (0.59)	1 (1.35)	10 (1.81)	0.005
Cerebrovascular disease	524 (11.62)	360 (11.84)	102 (12.13)	3 (4.05)	59 (10.67)	0.152
Dementia	27 (0.60)	17 (0.56)	6 (0.71)	1 (1.35)	3 (0.54)	0.562
Chronic pulmonary disease	211 (4.68)	120 (3.95)	44 (5.23)	9 (12.16)	38 (6.87)	<0.001
Connective tissue disease	75 (1.66)	51 (1.68)	10 (1.19)	4 (5.41)	10 (1.81)	0.084
Peptic ulcer disease	58 (1.29)	34 (1.12)	5 (0.59)	2 (2.70)	17 (3.07)	0.001
Mild liver disease	274 (6.08)	193 (6.35)	39 (4.64)	3 (4.05)	39 (7.05)	0.184
Diabetes, no chronic complications	1246 (27.63)	860 (28.28)	226 (26.87)	25 (33.78)	135 (24.41)	0.157
Diabetes, with chronic complications	30 (0.67)	18 (0.59)	6 (0.71)	0 (0.00)	6 (1.08)	0.525
Hemiplegia or paraplegia	210 (4.66)	130 (4.27)	46 (5.47)	1 (1.35)	33 (5.97)	0.107
Kidney disease	354 (7.85)	240 (7.89)	57 (6.78)	9 (12.16)	48 (8.68)	0.262
Malignant tumors without metastasis	240 (5.32)	157 (5.16)	44 (5.23)	3 (4.05)	36 (6.51)	0.600
Metastatic tumors	216 (4.79)	137 (4.51)	46 (5.47)	0 (0.00)	33 (5.97)	0.055
Moderate-to-severe liver disease	51 (1.13)	38 (1.25)	5 (0.59)	1 (1.35)	7 (1.27)	0.326
AIDS	65 (1.44)	32 (1.05)	18 (2.14)	4 (5.41)	11 (1.99)	0.003

<b>Characteristics</b>	<b>All patients (n=4509)</b>	<b>CSE with AAT (n=3041)</b>	<b>CSE with Delayed AAT (n=841)</b>	<b>CRE with AAT (n=74)</b>	<b>CRE with Delayed AAT (n=553)</b>	<b>P-value</b>
Septic shock	707 (15.68)	453 (14.90)	89 (10.58)	30 (40.54)	135 (24.41)	<0.001
<b>Charlson comorbidity index (CCI)</b>						
Mean score (SD)	1.45 (1.75)	1.40 (1.70)	1.50 (1.83)	1.50 (1.60)	1.62 (1.93)	0.043
Median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	0.379
Score $\geq$ 5	343 (7.61)	207 (6.81)	75 (8.92)	5 (6.76)	56 (10.13)	0.020
<b>Evidence of use on index day or day prior of</b>						
Corticosteroids	743 (16.48)	364 (11.97)	148 (17.60)	39 (52.70)	192 (34.72)	<0.001
Parenteral nutrition	121 (2.68)	48 (1.58)	30 (3.57)	10 (13.51)	33 (5.97)	<0.001
Vasoactive medications	748 (16.59)	379 (12.46)	138 (16.41)	44 (59.46)	187 (33.82)	<0.001
<b>Previous antibiotics</b>						
Carbapenems	449 (11.07)	240 (7.89)	62 (7.37)	45 (60.81)	152 (27.49)	<0.001
Amoxicillin/clavulanic acid	24 (0.53)	12 (0.39)	3 (0.36)	1 (1.35)	8 (1.45)	0.015
Piperacillin/tazobactam	344 (7.63)	154 (5.06)	50 (5.95)	24 (32.43)	116 (20.98)	<0.001
3rd generation cephalosporins	1627 (36.08)	972 (31.96)	280 (33.29)	52 (70.27)	323 (58.41)	<0.001
Fluoroquinolones	164 (3.64)	80 (2.63)	25 (2.97)	13 (17.57)	46 (8.32)	<0.001
Aminoglycosides	67 (1.49)	24 (0.79)	29 (3.45)	3 (4.05)	11 (1.99)	<0.001
Colistin	110 (2.44)	29 (0.95)	14 (1.66)	34 (45.95)	33 (5.97)	<0.001
Tigecycline	14 (0.31)	3 (0.10)	3 (0.36)	2 (2.70)	6 (1.08)	<0.001
Fosfomycin	65 (1.44)	25 (0.82)	13 (1.55)	12 (16.22)	15 (2.71)	<0.001

**Abbreviations:** AAT, appropriate antibiotic therapy; AIDS, acquired immune deficiency syndrome; BSI, bloodstream infection; CCI, Charlson Comorbidity Index; CRE, carbapenem-resistant Enterobacterales; CSE, carbapenem-susceptible Enterobacterales; CSMBS, Civil Servant Medical Benefit Scheme; IAI, intra-abdominal infection; ICU, intensive care unit; IQR, interquartile range; SD, standard deviation; SSS, Social Security Scheme; UCS, Universal Coverage Scheme; UTI, urinary tract infection