Supplementary Table 1. Baseline characteristics of the study participants.

	'Standard exposure' group (n=596)	'High exposure' group (n=604)	Overall (n=1200)
Age, years - median (IQR)	67 (58–75)	67 (58–76)	67 (58–76)
Male sex – no. (%)	333 (55·9%)	330 (54.6%)	663 (55.3%)
Body Mass Index, kg/m2 – median (IQR)	24.7 (22.0–27.8)	25.0 (22.5–28.7)	24.8 (22.2–27.9)
APACHE II Score - median (IQR)	18 (13–24)	18 (13–25)	18 (13–24)
Chronic co-morbidity* - no. (%)			
No chronic co-morbidities	102 (17.1)	123 (20.4)	225 (18.8)
Kidney function and electrolytes			
Creatinin, μmol/L - median (IQR)	119 (78, 197)	119 (75, 208)	119 (76, 202)
eGFR, mL/min/1.73m^2 – median (IQR)	51.4 (29.2, 80.5)	49.4 (25.4, 82.6)	50.2 (27.1, 81.5)
Carbamid, mmol/L - median (IQR)	10.3 (6.5, 17.0)	10.6 (6.3, 18.1)	10.5 (6.4, 17.4)
Na$^+$, mmol/l - median (IQR)	138 (134, 141)	137 (134, 141)	138 (134, 141)
K$^+$, mmol/l - median (IQR)	4.0 (3.7, 4.4)	4.0 (3.6, 4.5)	4.0 (3.6, 4.4)
pH - median (IQR)	7.29 (7.21–7.39)	7.29 (7.20–7.38)	7.29 (7.20–7.38)
Dialysis required, patients (%)	88 (14.8%)	86 (14.2%)	174 (14.5%)
Indicators of severity (non-renal)			
Temperature, ^{0}C - median (IQR)	37.2 (36.4–38.0)	37.3 (36.5–38.1)	37.3 (36.4–38.0)
Mean arterial pressure, mmHg - median (IQR)	71 (60–84)	72 (63–85)	71 (62–84)
Heart frequency - median (IQR)	100 (82–116)	100 (84–117)	100 (83–117)
Need for vasopressor/inotropic drug† - n (%)	315 (52.9)	326 (53.4)	641 (53.4)
Mechanical ventilation used - n (%)	401 (67.3%)	401 (66.4%)	802 (66.8%)
Biomarkers			
Alert-PCT **§** – no. (%)	279 (47.0)	312 (51.7)	591 (49.4)
Leukocytes, x10^9 – median (IQR)	13.0 (8.8–18.1)	12.4 (8.0–18.1)	12.8 (8.4–18.1)
C-reactive protein, mg/L – median (IQR)	131 (40–234)	137 (40–253)	135 (40–241)

Interquartile range (IQR). Acute Physiology and Chronic Health Evaluation II score (APACHE II) ranges from 0 to 71. *Chronic co-morbidity: Earlier diagnosed via hospital admission: heart failure, lung disease, cancer, diabetes, alcohol abuse, chronic infection, neurological disease, renal diseases, liver disease, gastro-intestinal disease, autoimmune disease, cancer and psychiatric disorders. †Vasopressors/inotropic drugs are considered to be epinephrine, nor-epinephrine, dopamine and dobutamine. ‡ Infections were rated according to the ACCP/SCCM definitions; investigators were trained in using them. §Alert-PCT: Procalcitonin-level not decreasing by at least 10% from the previous day and above 1.0 ng/ml. If only one measurement is available: Absolute procalcitonin-level above 1.0 ng/ml. A comprehensive baseline table is available in the primary publication from this material[13].

Supplementary Table 2. Consumption of antimicrobials during follow-up

	Standard exposure (n=596)	High exposure (n=604)	p-value
Consumption of antimicrobials			
Pip/tazo used within 28 days (DDD)	1893	2925	-
Proportion of days[a] followed where Pip/tazo was used	0.00 (0.00 – 0.33)	0.11 (0.00 – 0.56)	<0.001
Meropenem used within 28 days (DDD)	2174	2480	-
Proportion of days[a] followed where meropenem was used	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.07)	0.23
Cefuroxim used within 28 days (DDD)	4369	3390	-
Proportion of days[a] followed where cefuroxim was used	0.11 (0.00 – 0.39)	0.04 (0.00 – 0.29)	<0.001
Ciprofloxacin used within 28 days (DDD)	6210	8382	-
Proportion of days[a] followed where ciprofloxacin was used	0.21 (0.00 – 0.71)	0.33 (0.04 – 0.88)	<0.001
Number (%) ICU days spent with at least three antimicrobials	2721 (57.7%)	3570 (65.5%)	0.002

ICU: Intensive care unit. [a]This comparison was made with complete follow-up for 28 days (if patients were discharged from ICU, they were followed for antimicrobial use in all hospital admissions in Denmark). Pip/tazo: piperacillin/tazobactam. DDD: Defined Daily Dose administered within day 1-28. Parts of this table is also available in the primary publication on this material[13]. It is included in the present report since it is crucial for interpretation of the results.

Supplementary table 3: Cox proportional hazards models investigating predictors of mortality after ten days				
	Unadjusted analysis		**Multivariable analysis**	
Variable	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Treatment arm ('High exposure vs. 'Standard exposure)	0.97 (0.72, 1.31)	0.86	0.93 (0.69, 1.26)	0.63
Hospital:				
1	Ref	0.11	Ref	0.37
2	0.63 (0.19, 2.05)		0.50 (0.15, 1.66)	
3	0.54 (0.17, 1.75)		0.49 (0.15, 1.63)	
4	0.86 (0.26, 2.81)		0.65 (0.19, 2.21)	
5	0.56 (0.16, 1.88)		0.45 (0.13, 1.56)	
6	0.71 (0.21, 2.37)		0.63 (0.18, 2.12)	
7	0.79 (0.23, 2.72)		0.66 (0.18, 2.40)	
8	0.43 (0.11, 1.53)		0.34 (0.09, 1.26)	
9	0.23 (0.05, 1.02)		0.27 (0.06, 1.26)	
Gender (Female vs. Male)	0.80 (0.59, 1.08)	0.14	0.77 (0.57, 1.05)	0.10
Age (≥65 years vs. <65 years)	1.96 (1.42, 2.69)	<0.0001	1.86 (1.34, 2.58)	<0.0001
APACHE II score (≥20 vs. <20)	1.77 (1.31, 2.39)	<0.0001	1.35 (0.98, 1.87)	0.07
Infection at baseline (Severe Sepsis or septic shock vs Milder or no infection)	1.31 (0.97, 1.76)	0.08	1.17 (0.84, 1.64)	0.35
Surgical patient (Yes vs. No)	0.78 (0.57, 1.06)	0.11	0.76 (0.55, 1.05)	0.09
Date recruited (01/01/08 to 02/06/09 vs. 09/01/06 to 31/12/07)	1.11 (0.81, 1.53)	0.50	1.18 (0.84, 1.67)	0.34
eGFR ever <30 mL/min/1.73 m^2 over the first ten days (Yes vs. No)	1.81 (1.34, 2.45)	<0.0001	1.47 (1.06, 2.04)	0.02