Supplementary Online Content

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

eMethods

Patients

Both study intensive care units (ICUs) participated in a cluster randomized crossover trial conducted in 16 Dutch hospitals in which ICUs were randomized to start with either selective decontamination of the digestive tract (SDD) or selective oropharyngeal decontamination (SOD) for 12 months (after a wash-in period of 1 month)[1]. Academic Medical Center (AMC) participated from June 1 2010 to July 2012, University Medical Center (UMC) Utrecht from May 1 2010 – June 1 2012; outside these study periods both centers used SDD, which is standard of care in the Netherlands. SDD and SOD regimens have been described[1,2] and consisted of oropharyngeal application (every 6 hours) of a paste containing colistin, tobramycin, and amphotericin B, each in a 2% concentration (in patients receiving SDD and SOD), and administration (every 6 hours) of a 10-mL suspension containing colistin (100 mg), tobramycin (80 mg as sulfate), and amphotericin B (500 mg) via nasogastric tube (in patients receiving SDD). Topical antibiotics were applied until ICU discharge. In addition, cefotaxime (1 g 4 times daily) was administered intravenously during the first 4 days in the ICU as part of SDD but not as part of SOD.

Of all patients, the exact date and time of ICU-admission was known. Since it was not possible to set a time for the development of an infection, all infections were set to 0.00 hours of the day that they occurred. Subsequently, the onset of an ICU-acquired infection was calculated using the exact time of ICU admission and the timing of the ICU-acquired event, rounded for days.

Definition of comorbidities

Immunocompromise was defined as a medical history of immune deficiency, human immune deficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), or by the use of corticosteroids or antineoplastic medication. Cardiovascular insufficiency was defined as having a medical history of congestive heart failure, chronic cardiovascular disease, peripheral vascular disease or cerebrovascular disease. Malignancy was defined as a medical history of either non-metastatic solid tumor, metastatic malignancy or hematologic malignancy. Renal insufficiency was defined as a history of chronic renal insufficiency or chronic intermitted hemodialysis or continuous ambulatory peritoneal dialysis. Respiratory insufficiency was defined as chronic obstructive pulmonary disease or respiratory insufficiency in the medical history.

Microarray analysis and bioinformatics

For gene expression measurements, whole blood was collected in PAXgene™ tubes (Becton-Dickinson, Breda, the Netherlands) within 24 hours after ICU admission of 421 patients (461 admissions) enrolled between January 2011 and July 2012 with probable or definite infection according to criteria previously described[3] and at least one additional parameter described in the 2001 International Sepsis Definition Conference (eTable 1[4]). In addition, paired PAXgene™ tubes (admission and ICU-acquired event) were available from 19 patients who developed an ICU-acquired infection and from 9 patients who developed a non-infectious ICU-acquired complication (acute lung injury, n = 2; acute kidney injury, n = 6; acute myocardial infarction, n=1: these non-infectious complications were predefined in the study protocol and occurred at median day 3, interquartile range (IQR) 3-10 after ICU admission). Event samples were drawn within 24 hours around the development of the ICU-acquired event. PAXgene blood samples were also obtained from 42 healthy controls (median age 35 IQR 30-63 years; 57% male) after providing written informed consent.

Total RNA was isolated using the automated QIAcube machine (Qiagen, Venlo, the Netherlands) in combination with the blood mRNA kit (Qiagen) according to manufacturer's instructions. Quality and integrity of RNA was assessed by Nanodrop spectrophotometry (260:280nm) and bioanalysis (Agilent, Amstelveen, the Netherlands). RNA (RNA integrity number > 6.0) was processed and hybridized to the Human Genome U219 96-array plate using the GeneTitan^{R} instrument (Affymetrix) at the Cologne Center for Genomics, Cologne, Germany, as described by the manufacturer (Affymetrix). Raw data scans (.CEL files) were read into the R language and environment for statistical computing (version 2.15.1; R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Pre-processing and quality control was performed by using the *Affy* package version 1.36.1[5]. Array data were background corrected by Robust Multi-array Average, quantiles-normalized and summarized by medianpolish using the *expresso* function (*Affy* package). The resultant 49,386 probe intensities were filtered by means of a 0.5 variance cutoff using the genefilter method[6] to recover 24,646 expressed probes. The occurrence of non-experimental chip effects was evaluated by means of the Surrogate Variable Analysis (R package version 3.4.0) [7] and corrected by the empirical Bayes method *ComBat*[8]. The non-normalized and normalized *Molecular Diagnosis and Risk Stratification of Sepsis* (MARS) gene expression data sets are available at the Gene Expression Omnibus public repository of NCBI under accession number GSE65682.

The 24,646 probes were assessed for differential abundance in both admission samples discordant for ICU-acquired infections as well as paired admission and follow-up samples by means of the *limma* method (version 3.14.4)[9-11]. Throughout Benjamini-Hochberg (BH)[12] multiple comparison adjusted probabilities, correcting for the 24,646 probes (false discovery rate < 5%), defined significance. Ingenuity Pathway Analysis (Ingenuity Systems IPA, www.ingenuity.com) was used to evaluate the association to canonical signaling pathways stratifying genes by over- and under-expressed patterns. The Ingenuity gene knowledgebase was selected as reference and human species specified. All other parameters were default. Association significance was measured by Fisher's exact test BH-adjusted p-values.

Statistical analysis

All consecutive patient admissions were included in the cohort. The baseline characteristics age, sex, race, and comorbidities are shown for each first admission for sepsis (or a non-infectious condition). For patients admitted for sepsis after an admission for a non-infectious condition, the first sepsis admission was used. Survival status was calculated from the first ICU admission with the same admission reason (i.e., sepsis or non-infectious) of every patient, except for ICU mortality, for which all ICU admissions were used. For all other parameters, readmissions for the same admission reason were included as unique admissions.

All results are presented as numbers (percentages) for categorical variables, median and interquartile ranges [IQR] for non-parametric quantitative variables and mean and standard deviation (SD) for parametric quantitative variables. Continuous non-parametric data were analyzed using a Mann-Whitney *U* or Kruskal-Wallis test, categorical data were analyzed using a 2- tailed χ^2 or Fisher exact test, as appropriate. All continuous parametric data were analyzed using a *t*-test or analysis of variance when appropriate. All data were analyzed using R studio built under R version 3.0.2 (R Core Team 2013, Vienna, Austria)[13]. For population attributable mortality fraction analysis the R-package "mstate" was used.

For the analysis of Sequential Organ Failure Assessment (SOFA) scores during ICU stay a mixed-effects model was executed. In a mixed-effect model repeated measures within the same individual are taken into account. The mixed-effect model was tested in multiple ways, using both 10log transformed and non-log transformed SOFA scores. The SOFA score up to 2 day before the ICU-acquired event was used to overcome the effect of the event on outcome.

For all comparative percentages reported in the text of the main manuscript differences and 95% confidence intervals were calculated using R package *pairwiseCI.*

P<.05 (2-sided) was considered statistically significant.

Competing risk analysis

To identify risk factors for the development of an ICU-acquired infection we used a multivariable competing risk survival model. A multivariable competing risk analysis provides two measures of association: the cause specific hazard ratio (CSHR) which estimates the direct effect of the exposure of interest (i.e., severity of disease) on the various outcomes (i.e., ICU discharge, ICU mortality and the development of an ICU-acquired infection), and the subdistribution hazard ratio (SHR), which describes the risk for the development of an ICU-acquired infection while accounting for the competing events. Admission variables included in this model were quartiles of Acute Physiology and Chronic Health Evaluation IV (APACHE-IV) score, sex, age, admission type (medical versus surgical), the absolute number of organs failing at admission (ranging from 0-5), the use of either SDD or SOD, the comorbidities; a history of immunocompromised state, cardiovascular insufficiency, malignancy, renal and respiratory insufficiency, and the use of urinary catheter, central venous catheter, surgical drain, mechanical ventilation, renal replacement therapy and the use of corticosteroids before the event (ICU-acquired infection, mortality or discharge).

Multistate model for population attributable mortality fraction

The attributable mortality fraction (or population attributable fraction, PAF) can be interpreted as the proportion of ICU deaths that could theoretically be avoided if ICU-acquired infections could completely be prevented[14]. The PAF can be mathematically represented as: $PAF = [P(D) - P(D|E^-)]/ P(D)$, where P(D) is the overall probability of dying in the study population and $P(D|E^-)$ is the conditional probability of dying, given no exposure to an ICU-acquired infection. The absolute mortality difference is the total mortality in the study population minus the mortality in the population without an ICU-acquired infection. It can be calculated by multiplying the PAF and the overall mortality in the study population[15]. A multistate approach was used in order to estimate the population attributable fraction. A progressive disability model was fitted in order to account for the time dependency of the risk factor, the presence of competing risks (i.e., discharge or mortality without an ICU-acquired infection) at each time point, and the heterogeneity of the study population. The multistate model used is derived from a Markov model[16]. Quartiles of APACHE-IV scores and of age per specific patient population (i.e., sepsis and non-infectious) were used as co-variables. In this model, an estimator for the

population attributable mortality fraction can be derived in terms of the transition probabilities. The transition probabilities of a time-inhomogeneous Markov multistage model were estimated with the Aalen-Johansen estimator. The arrival time in a state (the past) was tested for significance for a given transitions (the future) by including it as a covariate in a Cox model for the transition hazards. Since the test was not significant, the Markov assumption was reasonable for our dataset. For this multivariable analysis only the first ICU-acquired infection was used. The population attributable mortality fraction was expressed as the percentage of ICU mortality caused by the ICU-acquired infections. Confidence intervals (CI) were calculated by bootstrap resampling (N=4000 at seed 2).

Missing data

Demographic, clinical and discharge data were imported in the data base from electronic medical records. Missing data or inconsistencies were checked and added manually by the research team. Records of comorbidities were also complete (the presence of each comorbidity was default set to 0 and could be actively set to 1). Patient race was unknown in 33 (2.1%) patients with a sepsis admission diagnosis and 51 (3.4%) patients with a non-infectious admission diagnosis. SOFA scores were missing in 75 (4.4%) admissions for sepsis and in 91 (4.7%) admissions for non-infectious disease. Lost to 1 year follow-up is reported below the corresponding tables. Missing data were not imputed.

eTable 1. Diagnostic criteria for sepsis in adults according to 2001 International Sepsis Definitions Conference[4]

Infection documented or suspected, and some of the following:
General variables
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C)
Heart rate >90 min^{-1} or >2 SD above the normal value for age
Tachypnea
Altered mental status
Significant edema or positive fluid balance (>20 mL/kg over 24 hrs)
Hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes
Inflammatory variables
Leukocytosis (WBC count >12.000 μL^{-1})
Leukopenia (WBC count <4000 μL^{-1})
Normal WBC count with >10% immature forms
Plasma C-reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic variables
Arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg)
SvO_2 >70%
Cardiac index >3.5 $L \bullet min^{-}1 \bullet m^{-2}$
Organ dysfunction variables
Arterial hypoxemia (PaO_2/FIO_2 <300)
Acute oliguria (urine output <0.5 $mL \bullet kg^{-1} \bullet hr^{-1}$ or 45 mmol/L for at least 2 hrs)
Creatinine increase >0.5 mg/dL
Coagulation abnormalities (INR >1.5 or aPTT >60 secs)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000 μL^{-1})
Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L)
Tissue perfusion variables
Hyperlactatemia (>1 mmol/L)
Decreased capillary refill or mottling

Abbreviations: aPTT: activated partial thromboplastin time; INR: international normalized ratio; MAP: mean arterial blood pressure; SBP: systolic blood pressure; SD: standard deviation; SvO_2: mixed venous oxygen saturation; WBC: white blood cell.

eTable 2. Causative pathogens of ICU-acquired infections after admission for sepsis

Gram-positive bacteria	**151 (45.2%)**	**Gram-negative bacteria**	**89 (26.6%)**
Staphylococcus epidermidis	49 (14.7%)	*Pseudomonas aeruginosa*	30 (9.0%)
Enterococcus faecium	40 (12.0%)	*Escherichia coli*	13 (3.9%)
Enterococcus faecalis	21 (6.3%)	*Klebsiella pneumoniae*	9 (2.7%)
Staphylococcus aureus	20 (6.0%)	*Stenothrophomas maltophilia*	9 (2.7%)
Enterococcus species	16 (4.8%)	*Bacteroides species*	6 (1.8%)
Clostridium difficile	2 (0.6%)	*Serratia marcescens*	5 (1.5%)
Corynebacterium species	2 (0.6%)	*Enterobacter cloacae*	4 (1.2%)
Streptococcus pneumoniae	1 (0.3%)	*Morganella species*	3 (0.9%)
		Pseudomonas species	2 (0.6%)
Virus	**33 (9.9%)**	*Haemophilus influenzae*	1 (0.3%)
Herpes simplex reactivation	13 (3.9%)	*Citrobacter species*	1 (0.3%)
Cytomegalovirus reactivation	7 (2.1%)	Gram-negative bacilli	1 (0.3%)
Primary herpes simplex virus	7 (2.1%)	*Klebsiella oxytoca*	1 (0.3%)
Other viruses	4 (1.2%)	*Enterobacter species*	1 (0.3%)
Adenovirus	2 (0.6%)	*Enterobacteriaceae*	1 (0.3%)
		Actinetobacter species	1 (0.3%)
		Proteus vulgaris	1 (0.3%)
Other	**8 (2.4%)**	**Fungi**	**32 (9.6%)**
Other pathogens	5 (1.5%)	Other fungi	12 (3.6%)
Polymicrobial or fecal flora	3 (0.9%)	*Candida albicans*	9 (2.7%)
		Candida glabrata	4 (1.2%)
Unknown	**82** (**24.5%**)	*Aspergillus fumigatus*	4 (1.2%)
		Candida species (not specified)	2 (0.6%)
		Candida kruseii	1 (0.3%)

Percentages depict the portion of ICU-acquired infections caused by the pathogen indicated. In total 313 pathogens were assigned to 334 ICU-acquired infections; in 49 (14.7%) of all ICU-acquired infections more than one pathogen was assigned as causative.

eTable 3. Admission diagnoses of patients with sepsis who did and those who did not develop an ICU-acquired infection

	ICU-acquired infection	No ICU-acquired infection	
	N= 232 (13.5%)	**N= 1487 (86.5%)**	***P***
Pulmonary tract	112 (48.3%)	778 (52.3%)	.26
CAP	66 (28.4%)	419 (28.2%)	.93
HAP	45 (19.4%)	349 (23.5%)	.18
VAP	1 (0.4%)	10 (0.7%)	>.99
Cardiovascular	17 (7.3%)	41 (2.8%)	.001
Bacteremia	12 (5.2%)	19 (1.3%)	.001
CRBSI	5 (2.2%)	22 (1.5%)	.55
Abdominal tract	44 (19.0%)	244 (16.4%)	.36
Abdominal infection	41 (17.7%)	226 (15.2%)	.37
Gastrointestinal infection	3 (1.3%)	18 (1.2%)	>.99
Neurological	5 (2.2%)	80 (5.4%)	.04
Brain abscess	0 (0%)	22 (1.5%)	.10
Primary meningitis	3 (1.3%)	30 (2.0%)	.61
Secondary meningitis	2 (0.9%)	26 (1.7%)	.42
Spinal Abscess	0 (0%)	2 (0.1%)	>.99
Skin	5 (2.2%)	57 (3.8%)	.26
Urinary tract	10 (4.3%)	72 (4.8%)	.75
Other	39 (16.8%)	215 (14.5%)	.37
Bone/joint infection	2 (0.9%)	16 (1.1%)	>.99
Endocarditis	10 (4.3%)	49 (3.3%)	.45
Mediastinitis	11 (4.7%)	48 (3.2%)	.26
Myocarditis	0 (0%)	4 (0.3%)	.65
Lung abscess	4 (1.7%)	15 (1.0%)	.50
Other/unknown infection	4 (1.7%)	29 (2.0%)	>.99
Oral infection	2 (0.9%)	12 (0.8%)	>.99
Pharyngitis	1 (0.4%)	18 (1.2%)	.37
Post-OP wound infection	1 (0.4%)	18 (1.2%)	.36
Sinusitis	0 (0%)	4 (0.3%)	.65
Viral infection	4 (1.7%)	2 (0.1%)	.002

Abbreviations: CAP: community-acquired pneumonia; CRBSI: catheter related blood stream infection; HAP: hospital-acquired pneumonia; Post-OP: post-operative; VAP: ventilator-associated pneumonia.

N is number of admissions

eTable 4A. Total sample size and crude number of admissions experiencing the outcome for competing risk analysis

Risk factors	Total sample size	Total number discharged	Total number deceased	Total number with ICU-AI
Admission	N = 1719	N = 1256	N = 231	N = 232
APACHE 1st quartile (<64) (reference)	451	389	24	38
APACHE 2nd quartile (64-80)	425	336	40	49
APACHE 3rd quartile (81-99)	424	300	61	63
APACHE 4th quartile (100-205)	419	231	106	82
Men	1049	767	130	152
Age (per 1 year)	1719	1256	231	232
Surgical admission	393	293	47	53
Organ failure (per number of organs failing ranging from 0-5)	1719	1256	231	232
SOD users	550	402	78	70
Chronic comorbidity				
Immunocompromised state	376	250	61	65
Cardiovascular insufficiency	428	317	53	58
Malignancy	368	258	64	46
Renal insufficiency	224	157	29	38
Respiratory insufficiency	322	229	40	53
Interventions during admission				
Urinary catheter	1631	1180	225	226
Central venous catheter	1397	970	210	217
Surgical drain	184	129	25	30
Mechanical ventilation	1598	1142	226	230
Renal replacement therapy	333	175	85	73
Hydrocortisone >200mg	769	489	142	138

All numbers in this table represent admissions

eTable 4B. Crude competing risk analysis for acquiring an ICU-acquired infection in patients with sepsis[a]

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Admission				
APACHE 1st quartile (<64) (reference)	1	1	1	1
APACHE 2nd quartile (64-80)	0.74 (0.64-0.86)	1.46 (0.88-2.43)	0.99 (0.65-1.51)	1.38 (0.90-2.10)
APACHE 3rd quartile (81-99)	0.64 (0.55-0.74)	2.15 (1.34-3.46)	1.23 (0.82-1.84)	1.81 (1.21-2.71)
APACHE 4th quartile (100-205)	0.46 (0.39-0.54)	3.60 (3.31-5.61)	1.48 (1.01-2.17)	2.44 (1.66-3.58)
Male gender	0.97 (0.87-1.09)	0.80 (0.62-1.04)	1.17 (0.89-1.53)	1.24 (0.94-1.62)
Age (per 1 year)	1.00 (0.9996-1.00)	1.01 (0.9883-1.02)	1.00 (0.99-1.01)	1.00 (0.99-1.00)
Surgical admission	1.12 (0.97-1.26)	0.92 (0.67-1.27)	1.09 (0.80-1.48)	1.00 (0.74-1.36)
Organ failure (per number of organs failing ranging from 0-5)	0.74 (0.70-0.79)	1.61 (1.42-1.82)	1.18 (1.04-1.35)	1.36 (1.20-1.54)
SOD use versus SDD	1.04 (0.92-1.17)	1.11 (0.85-1.46)	1.00 (0.75-1.32)	0.91 (0.69-1.21)
Chronic comorbidity				
Immunocompromised state	0.82 (0.71-0.94)	1.20 (0.89-1.61)	1.23 (0.92-1.64)	1.42 (1.07-1.90)
Cardiovascular insufficiency	0.95 (0.84-1.08)	0.84 (0.61-1.14)	0.91 (0.67-1.22)	1.00 (0.75-1.35)
Malignancy	0.91 (0.79-1.04)	1.35 (1.01-1.81)	0.84 (0.61-1.16)	0.90 (0.65-1.24)
Renal insufficiency	0.97 (0.82-1.14)	0.96 (0.65-1.42)	1.34 (0.94-1.90)	1.33 (0.94-1.89)
Respiratory insufficiency	0.96 (0.83-1.11)	0.91 (0.65-1.28)	1.25 (0.92-1.69)	1.31 (0.96-1.78)
Interventions during admission[b]				
Urinary catheter	0.62 (0.49-0.79)	1.64 (0.73-3.68)	1.31 (0.58-2.96)	2.08 (0.93-4.69)
Central venous catheter	0.49 (0.42-0.55)	1.57 (0.9989-2.46)	1.70 (1.00-2.87)	3.50 (2.08-5.91)

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Surgical drain	0.92 (0.76-1.01)	0.96 (0.63-1.45)	1.16 (0.78-1.70)	1.25 (0.85-1.84)
Mechanical ventilation	0.20 (0.16-0.24)	1.29 (0.53-3.16)	1.25 (0.31-5.10)	9.32 (2.32-37.48)
Renal replacement therapy	0.46 (0.39-0.64)	1.77 (1.35-2.31)	1.14 (0.86-1.50)	1.96 (1.49-2.59)
Hydrocortisone >200mg	0.59 (0.53-0.66)	1.56 (1.19-2.03)	1.24 (0.95-1.61)	1.87 (1.44-2.43)

Abbreviations: APACHE IV Acute Physiology And Chronic Health Evaluation; CI confidence intervals; CSHR cause specific hazard ratio; SHR subdistribution hazard ratio; SOD selective oropharyngeal decontamination; SDD Selective decontamination of the digestive tract.

[a]This table represents a univariable competing risk analysis in which the individual contribution of only one variable to the outcome of interest (discharge/mortality/ICU-acquired infection) was calculated and given as an cause specific hazard ratio or subdistribution hazard ratio with 95% CI. In this analysis the variables were incorporated in the model individually, and their crude contribution to outcome is given. In the competing risk analysis in the main manuscript (presented in Table 3), all these variables were combined in one model.

A multivariable competing risk analysis provides two measures of association: the cause specific hazard ratio which estimates the direct effect of the exposure of interest (i.e., severity of disease) on the various outcomes (i.e., ICU discharge, ICU mortality and the development of an ICU-acquired infection), and the subdistribution hazard ratio, which describes the risk for the development of an ICU-acquired infection while accounting for the competing events. A lower cause specific hazard ratio for discharge means that there is a lower hazard for discharge, in other words a higher likelihood for longer ICU stays.
In patients with multiple ICU-acquired infections, only the first ICU-acquired infection was used.

[b] All interventions were included until the onset of the event .

eTable 5A. Multivariate competing risk analysis for acquiring an ICU-acquired infection in patients with sepsis (only first admissions included, n=1504)[a]

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Admission				
APACHE 1st quartile (<64) (reference)	1	1	1	1
APACHE 2nd quartile (64-80)	0.89 (0.75-1.06)	1.22 (0.70-2.11)	1.04 (0.63-1.71)	1.29 (0.79-2.10)
APACHE 3rd quartile (81-100)	0.82 (0.68-0.98)	1.46 (0.86-2.49)	1.30 (0.79-2.13)	1.66 (1.03-2.69)
APACHE 4th quartile (101-205)	0.69 (0.56-0.84)	1.85 (1.08-3.18)	1.53 (0.93-2.52)	2.12 (1.30-3.47)
Men	0.95 (0.84-1.08)	0.79 (0.60-1.05)	1.09 (0.80-1.47)	1.19 (0.88-1.60)
Age (per 1 year)	1.01 (1.00-1.01)	1.02 (1.00-1.03)	0.99 (0.98-1.01)	0.99 (0.98-0.996)
Surgical admission	1.04 (0.90-1.20)	0.91 (0.64-1.30)	1.11 (0.79-1.57)	1.12 (0.80-1.57)
Organ failure (per number of organs failing ranging from 0-5)	0.95 (0.88-1.04)	1.48 (1.24-1.76)	1.16 (0.97-1.40)	1.04 (0.87-1.23)
SOD use versus SDD	1.09 (0.96-1.24)	0.98 (0.73-1.33)	1.02 (0.75-1.38)	0.96 (0.71-1.30)
Chronic comorbidity				
Immunocompromised state	1.11 (0.94-1.31)	0.99 (0.69-1.41)	1.10 (0.77-1.56)	1.06 (0.75-1.50)
Cardiovascular insufficiency	0.99 (0.85-1.15)	0.82 (0.58-1.16)	0.81 (0.57-1.15)	0.86 (0.60-1.21)
Malignancy	1.07 (0.92-1.25)	1.29 (0.93-1.79)	0.76 (0.52-1.10)	0.68 (0.47-0.98)
Renal insufficiency	1.13 (0.91-1.40)	0.80 (0.51-1.26)	1.68 (1.11-2.55)	1.49 (0.99-2.23)
Respiratory insufficiency	1.02 (0.87-1.20)	0.96 (0.66-1.40)	1.40 (0.996-1.98)	1.49 (1.05-2.11)
Interventions during admission[b]				
Urinary catheter	0.76 (0.59-0.98)	1.25 (0.55-2.84)	1.27 (0.56-2.92)	1.63 (0.72-3.71)
Central venous catheter	0.67 (0.57-0.79)	0.85 (0.50-1.44)	1.39 (0.74-2.59)	2.73 (1.49-4.99)

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Surgical drain	1.06 (0.85-1.32)	0.91 (0.56-1.46)	1.12 (0.70-1.80)	1.11 (0.70-1.78)
Mechanical ventilation	0.23 (0.18-0.30)	0.92 (0.33-2.54)	2.15 (0.29-15.75)	10.75 (1.50-77.15)
Renal replacement therapy	0.54 (0.44-0.67)	1.13 (0.79-1.63)	0.77 (0.53-1.12)	1.17 (0.80-1.70)
Hydrocortisone >200mg	0.76 (0.66-0.87)	1.00 (0.72-1.39)	1.05 (0.76-1.45)	1.38 (1.00-1.91)

Abbreviations: APACHE IV Acute Physiology And Chronic Health Evaluation; CI confidence intervals; CSHR cause specific hazard ratio; SHR subdistribution hazard ratio; SOD selective oropharyngeal decontamination; SDD Selective decontamination of the digestive tract.

[a] A multivariable competing risk analysis provides two measures of association: the cause specific hazard ratio which estimates the direct effect of the exposure of interest (i.e., severity of disease) on the various outcomes (i.e., ICU discharge, ICU mortality and the development of an ICU-acquired infection), and the subdistribution hazard ratio, which describes the risk for the development of an ICU-acquired infection while accounting for the competing events. A lower cause specific hazard ratio for discharge means that there is a lower hazard for discharge, in other words a higher likelihood for longer ICU stays. Admission variables included in this model were quartiles of Acute Physiology and Chronic Health Evaluation (APACHE)-IV score, sex, age, admission type (medical versus surgical), the absolute number of organs failing at admission (ranging from 0-5), the use of either SDD or SOD, the comorbidities; a history of immunocompromised state, cardiovascular insufficiency, malignancy, renal and respiratory insufficiency, and the use of urinary catheter, central venous catheter, surgical drain, mechanical ventilation, renal replacement therapy and the use of corticosteroids before the event (ICU-acquired infection, mortality or discharge).
In patients with multiple ICU-acquired infections, only the first ICU-acquired infection was used.

[b] All interventions were included until the onset of the event.

eTable 5B. Multivariate competing risk analysis for acquiring an ICU-acquired infection in patients with sepsis (only patients with one admission included, n=1333)[a]

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Admission				
APACHE 1st quartile (<64) (reference)	1	1	1	1
APACHE 2nd quartile (64-80)	0.91 (0.76-1.09)	1.14 (0.66-1.97)	1.17 (0.66-1.89)	1.35 (0.81-2.26)
APACHE 3rd quartile (81-99)	0.80 (0.66-0.98)	1.44 (0.84-2.46)	1.47 (0.87-2.48)	1.86 (1.12-3.09)
APACHE 4th quartile (100-205)	0.69 (0.56-0.86)	1.98 (1.16-3.39)	1.70 (1.01-2.87)	2.20 (1.31-3.69)
Male gender	0.97 (0.85-1.11)	0.81 (0.61-1.08)	1.16 (0.84-1.60)	1.28 (0.94-1.76)
Age (per 1 year)	1.01 (1.00-1.01)	1.01 (1.00-1.02)	0.99 (0.98-1.01)	0.98 (0.97-0.995)
Surgical admission	1.02 (0.87-1.20)	1.02 (0.71-1.45)	1.11 (0.77-1.61)	1.12 (0.78-1.61)
Organ failure (per number of organs failing ranging from 0-5)	0.94 (0.86-1.03)	1.47 (1.24-1.75)	1.16 (0.96-1.41)	1.02 (0.85-1.22)
SOD use versus SDD	1.12 (0.98-1.29)	0.98 (0.72-1.31)	1.02 (0.74-1.41)	0.94 (0.68-1.29)
Chronic comorbidity				
Immunocompromised state	1.08 (0.90-1.30)	1.00 (0.70-1.42)	1.05 (0.73-1.53)	1.03 (0.71-1.49)
Cardiovascular insufficiency	0.97 (0.82-1.13)	0.81 (0.57-1.15)	0.76 (0.52-1.10)	0.83 (0.57-1.21)
Malignancy	1.05 (0.89-1.24)	1.23 (0.89-1.70)	0.78 (0.53-1.15)	0.73 (0.50-1.07)
Renal insufficiency	1.08 (0.85-1.37)	0.86 (0.54-1.36)	1.85 (1.19-2.87)	1.62 (1.05-2.50)
Respiratory insufficiency	1.03 (0.87-1.22)	1.01 (0.69-1.48)	1.34 (0.92-1.95)	1.42 (0.97-2.06)
Interventions during admission[b]				
Urinary catheter	1.78 (0.59-1.04)	1.23 (0.54-2.80)	1.34 (0.54-3.33)	1.62 (0.66-3.98)

Risk factors	Cause-Specific Hazard Ratio (95% CI)			ICU-acquired infection Subdistribution Hazard Ratio (95% CI)
	Discharge	Mortality	ICU-acquired infection	
Central venous catheter	0.67 (0.56-0.79)	0.89 (0.53-1.50)	1.69 (0.86-3.33)	3.32 (1.92-6.41)
Surgical drain	1.07 (0.84-1.38)	1.01 (0.63-1.63)	1.10 (0.65-1.87)	1.03 (0.61-1.74)
Mechanical ventilation	0.23 (0.18-0.30)	0.89 (0.32-2.46)	2.14 (0.29-15.72)	9.83 (1.37-70.58)
Renal replacement therapy	0.53 (0.42-0.67)	1.16 (0.81-1.67)	0.77 (0.52-1.25)	1,12 (0.75-1.58)
Hydrocortisone >200mg	0.78 (0.67-0.90)	0.97 (0.70-1.39)	0.91 (0.65-1.28)	1.25 (0.90-1.75)

Abbreviations: APACHE IV Acute Physiology And Chronic Health Evaluation; CI confidence intervals; CSHR cause specific hazard ratio; SHR subdistribution hazard ratio; SOD selective oropharyngeal decontamination; SDD Selective decontamination of the digestive tract.

[a] A multivariable competing risk analysis provides two measures of association: the cause specific hazard ratio which estimates the direct effect of the exposure of interest (i.e., severity of disease) on the various outcomes (i.e., ICU discharge, ICU mortality and the development of an ICU-acquired infection), and the subdistribution hazard ratio, which describes the risk for the development of an ICU-acquired infection while accounting for the competing events. A lower cause specific hazard ratio for discharge means that there is a lower hazard for discharge, in other words a higher likelihood for longer ICU stays. Admission variables included in this model were quartiles of Acute Physiology and Chronic Health Evaluation (APACHE)-IV score, sex, age, admission type (medical versus surgical), the absolute number of organs failing at admission (ranging from 0-5), the use of either SDD or SOD, the comorbidities; a history of immunocompromised state, cardiovascular insufficiency, malignancy, renal and respiratory insufficiency, and the use of urinary catheter, central venous catheter, surgical drain, mechanical ventilation, renal replacement therapy and the use of corticosteroids before the event (ICU-acquired infection, mortality or discharge).
In patients with multiple ICU-acquired infections, only the first ICU-acquired infection was used.

[b] All interventions were included until the onset of the event.

eTable 6. Sensitivity and subgroup analyses of incidence and population attributable mortality fraction of ICU-acquired infections in patients admitted with sepsis

Admission diagnosis	Number		Incidence of ICU-acquired infections	Day 30-Attributable mortality fraction (95% CI)	Day 60-Attributable mortality fraction (95% CI)
	Admissions	Patients			
Sepsis	1719	1504	232 (13.5%)	5.5% (-0.3%-11.3%)	10.9% (0.9%-20.9%)
Severe sepsis	1530	1353	218 (14.2%)	4.8% (-1.3%-10.9%)	10.1% (-1.0%-21.1%)
Septic shock	583	549	104 (17.8%)	4.8% (-5.8%-15.5%)	7.7% (-11.6%-27.1%)
Sepsis with *probable* or *definite* infection likelihood	1237	1089	178 (14.4%)	7.0% (0.4%-13.6%)	12.7% (0.3%-25.1%)
Sepsis readmissions excluded, only first admissions	1504	1504	199 (13.2%)	4.6% (-1.4%-10.8%)	9.7% (-1.1%-20.5%)
Sepsis, only patients with one admission	1333	1333	180 (13.5%)	4.4% (-1.9%-10.7%)	9.1% (-1.9%-20.1%)

Abbreviation: CI: confidence intervals, ICU : Intensive Care Unit

Note : population attributable mortality fraction results in which 95% CI cross zero are statistically not significant.

eTable 7. Baseline characteristics and outcome of patients who acquired catheter-associated blood stream infection, ventilator-associated pneumonia or abdominal infection while on the ICU[a]

	No ICU-acquired infection	CRBSI	VAP	Abdominal	Other ICU-acquired infection	
PATIENTS	**1305 (86.8%)**	**59 (3.9%)**	**46 (3.1%)**	**25 (1.7%)**	**69 (4.6%)**	***P***
Demographics						
Age (years)	60.1 (15.4)	59.4 (12.9)	54.0 (18.2)	63.4 (11.7)	60.2 (14.5)	.13
Male gender	796 (61.0%)	41 (69.5%)	28 (60.9%)	16 (64.0%)	43 (62.3%)	.78
White race	1161 (89.0%)	53 (89.8%)	40 (87.0%)	24 (96.0%)	61 (88.4%)	.92
Chronic comorbidity						
None	356 (27.3%)	10 (16.9%)	16 (34.8%)	8 (32.0%)	18 (261%)	.30
Charlson comorbidity index	4 [2-6]	4 [2-6]	3 [2-5]	4 [3-6]	4 [2-5]	.34
ADMISSIONS	**1487 (86.5%)**	**74 (4.7%)**	**54 (3.5%)**	**44 (2.9%)**	**84 (5.3%)**	
Medical	1147 (77.1%)	65 (87.8%)	44 (81.5%)	24 (54.5%)*	65 (77.4%)	.01
Surgical	340 (22.9%)	9 (12.2%)	10 (18.5%)	20 (45.5%)	19 (22.6%)	
Readmission	182 (12.2%)	15 (20.3%)	8 (14.8%)	19 (43.2%)*	15 (17.9%)	<.001
Severity of disease						
APACHE IV score	79 [62-100]	93 [83-112]*	88 [63-103]	92 [78-112]*	82 [68-106]	<.001
SOFA score	7 [4-9]	9 [7-11]*	7 [5-9]	10 [8-12]*	8 [4-10]	<.001
Severe sepsis	1312 (88.2%)	73 (98.6%)	52 (96.3%)	44 (100.0%)	73 (86.9%)	.07
Septic shock	479 (32.2%)	39 (52.7%)*	21 (38.9%)	31 (70.5%)*	39 (52.7%)	<.001
Treatment interventions before event						

	No ICU-acquired infection	CRBSI	VAP	Abdominal	Other ICU-acquired infection	
Urinary catheter	1405 (94.5%)	73 (98.6%)	52 (96.3%)	43 (97.7%)	81 (96.4%)	.39
Central venous catheter	1180 (79.4%)	73 (98.6%)*	50 (92.6%)*	44 (100.0%)*	74 (88.1%)	<.001
Surgical drain	154 (10.4%)	8 (10.8%)	3 (5.6%)	17 (38.6%)*	7 (8.3%)	<.001
Mechanical ventilation	1368 (92.0%)	74 (100.0%)	54 (100.0%)	44 (100.0%)	82 (97.6%)	.004
Renal replacement therapy	260 (17.5%)	30 (40.5%)	15 (27.8%)	20 (45.5%)*	20 (23.8%)	<.001
Corticosteroid use						
Any hydrocortisone use[b]	828 (55.7%)	61 (82.4%)*	33 (61.1%)	39 (88.6%)*	53 (63.1%)	<.001
Hydrocortisone[b] > 200mg/day	631 (42.4%)	51 (68.9%)*	27 (50.0%)	33 (75.0%)*	47 (56.0%)*	<.001
SDD use[c]	1007 (67.7%)	53 (71.6%)	29 (53.7%)	35 (79.5%)	61 (72.6%)	.06
Outcome						
Length of ICU stay (days)	5 [3-9]	28 [19-40]*	29 [18-44]*	29 [15-38]*	18 [13-26]*	<.001
Length of hospital stay (days)	26 [13-49]	60 [40-84]*	58 [33-83]*	62 [23-85]*	42 [25-64]*	<.001
Complications						
None	1241 (83.5%)	28 (37.8%)*	13 (24,1%)*	13 (29.5%)*	48 (57.1%)*	<.001
Acute kidney injury	129 (8.7%)	16 (21.6%)*	19 (35.2%)*	12 (27.3%)*	18 (21.4%)*	<.001
Acute lung injury	61 (4.1%)	11 (14.9%)*	12 (22.2%)*	7 (15.9%)*	5 (6.0%)	<.001
Discharge location						.002
Clinical ward	1195 (80.4%)	46 (62.2%)	33 (61.1%)	27 (61.4%)	52 (61.9%)	
Deceased	231 (15.5%)	25 (33.8%)	20 (37.0%)	16 (36.4%)	30 (35.7%)	
Home	6 (0.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Other/unknown	55 (3.7%)	3 (4.1%)	1 (1.9%)	1 (2.3%)	2 (2.4%)	

	No ICU-acquired infection	CRBSI	VAP	Abdominal	Other ICU-acquired infection	
Mortality						
ICU[d]	231 (15.5%)	25 (33.8%)*	20 (37.0%)*	16 (36.4%)*	30 (35.7%)*	<.001
Hospital[e]	351 (26.9%)	27 (45.8%)*	21 (45.7%)*	17 (68.0%)*	33 (47.8%)*	<.001
30 days[e]	320 (24.5%)	16 (27.1%)	13 (28.3%)	10 (40.0%)	24 (34.8%)	.13
60 days[e]	381 (29.1%)	25 (42.4%)	17 (37.0%)	15 (60.0%)*	31 (44.9%)*	.001
90 days[e]	420 (32.2%)	29 (49.2%)*	19 (41.3%)	17 (68.0%)*	34 (49.3%)*	<.001
1 year[e,f]	544 (41.7%)	32 (54.2%)	23 (50.0%)	17 (68.0%)*	37 (53.6%)	.002

Abbreviations: APACHE IV: Acute Physiology And Chronic Health Evaluation; CRBSI, catheter related blood stream infection; ICU: intensive care unit; SDD: selective decontamination of the digestive tract; SOFA: sequential organ failure score; VAP, ventilator-associated pneumonia.
Values are given as numbers (%), mean (standard deviation) or median [interquartile ranges].

Multiple ICU-acquired infections could occur in one patient during the same ICU stay: during 21 admissions both a CRBSI and a VAP were diagnosed; during 11 admissions both a CRBSI and an abdominal ICU-acquired infection were diagnosed; during 7 admissions both a VAP and an abdominal infection were diagnosed.
[a]The Charlson comorbidity index consists of points for multiple pre-existing comorbid diseases combined with points for age [17]. An increase in Charlson comorbidity index represents more (or more severe) pre-existing comorbid diseases and/or increased age. APACHE IV score is calculated using pre-existing comorbidities, acute diagnosis and acute physiology variables[18]. Increases in APACHE IV score are associated with increased risk for mortality. SOFA scores can range from 0-20 and consist of 0-4 point scale for SOFA circulation, coagulation, liver, renal and respiration. An increase in SOFA score represents more severe organ failure.
P values represent the overall significance of differences between the five groups (using a Kruskal-Wallis test for continuous non-parametric data, a two tailed Chi square or Fishers exact test for categorical data and analysis of variance for continuous parametric data); *depicts significance versus no ICU-acquired infection using a Dunn's test of multiple comparisons using rank sums.
[b] Use of hydrocortisone or its equivalent (hydrocortisone dose = 4 x prednisolone dose, 5 x methylprednisolone dose, 25 x dexamethasone dose).
[c] Patients not on SDD received selective oropharyngeal decontamination.
[d] ICU mortality was calculated using all ICU admissions for sepsis.
[e] Follow up data were calculated using the first ICU-admission for sepsis of each patient during the study period; readmissions were not included in this analysis.
[f] 40 patients were lost to 1 year follow up: 2.4% in patients with sepsis and no ICU-acquired infection, 5.1% in patients with catheter related bloodstream infection, 2.2% in patients with ventilator-associated pneumonia, 8.0% in patients with abdominal infection and 4.3% in patients with other ICU-acquired infections (*P*=.21).

eTable 8. Baseline characteristics and outcome of patients with sepsis included in the whole genome expression analyses[a]

	ICU-acquired infection	No ICU-acquired infection	
PATIENTS	**59 (14.0%)**	**362 (86.0%)**	***P***
Demographics			
Age (years)	61.8 (14.2)	60.8 (14.9)	.61
Male gender	38 (64.4%)	199 (55.0%)	.21
White race	51 (86.4%)	320 (88.4%)	.91
Chronic comorbidity			
None	16 (27.1%)	106 (29.3%)	.75
Charlson comorbidity index	4 [3-6]	4 [2-6]	.29
ADMISSIONS	**64 (13.9%)**	**397 (86.1%)**	
Medical	50 (78.1%)	294 (74.1%)	.78
Surgical	14 (21.9%)	103 (25.9%)	
Readmission	5 (7.8%)	35 (8.8%)	.81
Severity of disease			
APACHE IV score	91 [75-113]	81 [66-99]	.01
SOFA score	9 [6-10]	8 [5-10]	.01
Severe sepsis	63 (98.4%)	351 (88.4%)	.17
Septic shock	30 (46.9%)	156 (39.3%)	.27
Treatment interventions before event			
Urinary catheter	62 (96.9%)	381 (96.0%)	>.99
Central venous catheter	63 (98.4%)	346 (87.2%)	.01
Surgical drain	10 (15.6%)	61 (15.4%)	>.99
Mechanical ventilation	64 (100.0%)	376 (94.7%)	.09
Renal replacement therapy	21 (32.8%)	86 (21.7%)	.05
Corticosteroid use			
Any hydrocortisone use[b]	49 (76.6%)	252 (63.5%)	.05
Hydrocortisone[b] > 200mg/day	40 (62.5%)	204 (51.4%)	.10
SDD use[c]	30 (46.9%)	181 (45.6%)	.90
Outcome			
Length of ICU stay (days)	23 [15-33]	6 [4-10]	<.001
Length of hospital stay (days)	45 [27-78]	27 [15-56]	<.001
Complications			
None	18 (28.1%)	321 (80.9%)	<.001
Acute kidney injury	18 (28.1%)	40 (10.1%)	<.001
Acute lung injury	11 (17.2%)	15 (3.8%)	.001

	ICU-acquired infection	No ICU-acquired infection	
Discharge location			.001
Clinical ward	38 (59.4%)	320 (80.6%)	
Deceased	25 (39.1%)	64 (16.1%)	
Home	0 (0.0%)	2 (0.5%)	
Other/unknown	1 (1.6%)	11 (2.8%)	
Mortality			
ICU[d]	25 (39.1%)	64 (16.1%)	<.001
Hospital[e]	32 (54.2%)	107 (29.6%)	.001
30 days[e]	22 (37.3%)	91 (25.1%)	.08
60 days[e]	30 (50.8%)	109 (30.1%)	.004
90 days[e]	33 (55.9%)	119 (32.9%)	.002
1 year[e,f]	34 (57.6%)	159 (43.9%)	.04

Abbreviations: APACHE IV: Acute Physiology And Chronic Health Evaluation; ICU: intensive care unit; SDD: selective decontamination of the digestive tract; SOFA: sequential organ failure score.
Values are given as numbers (%), mean (standard deviation) or median [interquartile range].

[a]The Charlson comorbidity index consists of points for multiple pre-existing comorbid diseases combined with points for age [17]. An increase in Charlson comorbidity index represents more (or more severe) pre-existing comorbid diseases and/or increased age. APACHE IV score is calculated using pre-existing comorbidities, acute diagnosis and acute physiology variables[18]. Increases in APACHE IV score are associated with increased risk for mortality. SOFA scores can range from 0-20 and consist of 0-4 point scale for SOFA circulation, coagulation, liver, renal and respiration. An increase in SOFA score represents more severe organ failure.
[b] Use of hydrocortisone or its equivalent (hydrocortisone dose = 4 x prednisolone dose, 5 x methylprednisolone dose, 25 x dexamethasone dose).
[c] Patients not on SDD received selective oropharyngeal decontamination.
[d] ICU mortality was calculated using all ICU admissions for sepsis.
[e] Follow up data were calculated using the first ICU-admission for sepsis of each patient during the study period; readmissions were not included in this analysis
[f] 3 patients were lost to 1 year follow up 1.7% of patients with who developed an ICU-acquired infection and 0.6% of patients who did not develop and ICU-acquired infection.

eTable 9. Ingenuity pathway analysis of the common over-expressed and under-expressed genes in patients who developed an ICU-acquired infection and those who did not

Over-expressed pathways	-log (BH) *p*
IL-10 Signaling	2.9
PPARα/RXRα Activation	2.9
IL-8 Signaling	2.9
Toll-like Receptor Signaling	2.2
Role of Tissue Factor in Cancer	2.2
IL-1 Signaling	2.2
Mitochondrial Dysfunction	2.1
Glioma Invasiveness Signaling	2.0
Hypoxia Signaling in the Cardiovascular System	1.7
IL-6 Signaling	1.7

Under-expressed pathways	-log (BH) *p*
EIF2 Signaling	20.3
Regulation of eIF4 and p70S6K Signaling	13.1
mTOR Signaling	13.1
Calcium-induced T Lymphocyte Apoptosis	9.5
iCOS-iCOSL Signaling in T Helper Cells	9.1
B Cell Development	7.0
T Cell Receptor Signaling	5.7
Purine Nucleotides De Novo Biosynthesis II	4.4
DNA Methylation and Transcriptional Repression Signaling	4.0
Antigen Presentation Pathway	4.0

Ingenuity pathway analysis of the common over-expressed and under-expressed genes in patients who did and those who did not develop an ICU-acquired infection revealed significant associations (Fisher's exact Benjamini-Hochberg (BH) $p < 0.05$) to distinct biological pathways.

eTable 10. Baseline characteristics and outcome of patients admitted with a non-infectious condition stratified to the development of an ICU-acquired infection or not[a]

	ICU-acquired infection	No ICU-acquired infection	
PATIENTS	**277 (15.2%)**	**1548 (84.8%)**	***P***
Demographics			
Age (years)	59.4 (16.6)	58.4 (17.0)	.33
Male gender	182 (65.7%)	946 (61.1%)	.17
White race	251 (90.6%)	1384 (89.4%)	.81
Chronic comorbidity			
None	88 (31.8%)	536 (34.6%)	.36
Charlson comorbidity index	4 [2-5]	3 [2-5]	.10
ADMISSIONS	**291 (15.1%)**	**1630 (84.9%)**	
Medical	111 (38.1%)	802 (49.2%)	.002
Surgical	180 (61.9%)	828 (50.8%)	
Readmission	14 (4.8%)	82 (5.0%)	.90
Severity of disease on admission			
APACHE IV score	75 [57-92]	65 [49-87]	<.001
SOFA score	7 [5-9]	6 [3-8]	<.001
Organ failure	254 (87.3%)	1330 (81.6%)	.13
Shock	111 (38.1%)	406 (24.9%)	<.001
Treatment interventions before event			
Urinary catheter	286 (98.3%)	1551 (95.2%)	.02
Central venous catheter	238 (81.8%)	1152 (70.7%)	<.001
Surgical drain	9 (3.1%)	34 (2.1%)	.39
Mechanical ventilation	285 (97.9%)	1507 (92.5%)	<.001
Renal replacement therapy	61 (21.0%)	138 (8.5%)	<.001
Corticosteroid use			
Any hydrocortisone use[b]	134 (46.0%)	516 (31.7%)	<.001
Hydrocortisone[b] > 200mg/day	92 (31.6%)	346 (21.2%)	<.001
SDD use[c]	201 (69.1%)	1227 (75.3%)	.03
Outcome			
Length of ICU stay (days)	13 [9-22]	3 [3-7]	<.001
Length of hospital stay (days)	29 [16-49]	16 [9-30]	<.001
Complications			
None	171 (58.8%)	1440 (88.3%)	<.001
Acute kidney injury	62 (21.3%)	135 (8.3%)	<.001

	ICU-acquired infection	No ICU-acquired infection	
Acute lung injury	47 (16.2%)	23 (1.4%)	<.001
Discharge location			
Clinical ward	203 (69.8%)	1370 (84.0%)	.001
Deceased	76 (26.1%)	184 (11.3%)	
Home	2 (0.7%)	8 (0.5%)	
Other/unknown	10 (3.4%)	68 (4.2%)	
Mortality			
ICU[d]	76 (26.1%)	184 (11.3%)	<.001
Hospital[e]	100 (36.1%)	309 (20.0%)	<.001
30 days[e]	79 (28.5%)	303 (19.6%)	.002
60 days[e]	106 (38.3%)	347 (22.4%)	<.001
90 days[e]	111 (40.1%)	368 (23.8%)	<.001
1 year[e,f]	130 (46.9%)	465 (30.0%)	<.001

Abbreviations: APACHE IV: Acute Physiology And Chronic Health Evaluation; ICU: intensive care unit; SDD: selective decontamination of the digestive tract; SOFA: sequential organ failure score.
Values are given as numbers (%), mean (standard deviation) or median [interquartile range]

[a]The Charlson comorbidity index consists of points for multiple pre-existing comorbid diseases combined with points for age [17]. An increase in Charlson comorbidity index represents more (or more severe) pre-existing comorbid diseases and/or increased age. APACHE IV score is calculated using pre-existing comorbidities, acute diagnosis and acute physiology variables[18]. Increases in APACHE IV score are associated with increased risk for mortality.
SOFA scores can range from 0-20 and consist of 0-4 point scale for SOFA circulation, coagulation, liver, renal and respiration. An increase in SOFA score represents more severe organ failure.
[b] Use of hydrocortisone or its equivalent (hydrocortisone dose = 4 x prednisolone dose, 25 x dexamethasone dose, 5 x methylprednisolone dose).
[c] Patients not on SDD received SOD.
[d] ICU mortality was calculated using all ICU admissions for non-infectious conditions.
[e] Follow up data were calculated using the first ICU-admission for sepsis of each patient during the study period; readmissions were not included in this analysis.
[f] 67 patients were lost to 1 year follow up: 5.4% of patients who developed an ICU-acquired infection and 3.6% of patients who did not develop an ICU-acquired infection (*P*=.17).

eTable 11. Characteristics of all ICU-acquired infections after admission for a non-infectious condition

Number of admissions associated with an ICU-acquired infection	291 (15.1%)
Number of ICU-acquired infections	366
Number of admissions associated with multiple ICU-acquired infections	53 (18.2%)
Day of first ICU-acquired infection	4 [3-7]
Source of infection	
Pulmonary	**177 (48.4%)**
Hospital-acquired pneumonia	53 (14.5%)
Ventilator-associated pneumonia	124 (33.9%)
Cardiovascular	**71 (19.4%)**
Bacteremia	10 (2.7%)
Catheter related bloodstream infection	61 (16.7%)
Abdominal	**32 (8.7%)**
Abdominal infection	28 (7.7%)
Gastrointestinal infection	4 (1.1%)
Neurological	**29 (7.9%)**
Brain abscess	1 (0.3%)
Primary meningitis	0 (0.0%)
Secondary meningitis	28 (7.7%)
Skin	**13 (3.6%)**
Urinary tract	**6 (1.6%)**
Other[a]	**38 (10.4%)**
Causative pathogen	420
Gram-positive bacteria	124 (33.9%)
Gram-negative bacteria	122 (33.3%)
Fungi	22 (6.0%)
Viral	2 (0.5%)
Other	10 (2.7%)
Unknown	137 (37.4%)

Abbreviations: ICU: intensive care unit.
Values are given as numbers (%), mean (standard deviation) or median [interquartile range].

Percentages depict the portion of ICU-acquired infections (N = 366) caused by the pathogen group indicated.
In total 280 pathogens were assigned to 366 ICU-acquired infections; in 41 (11.2%) of all ICU-acquired infections more than one pathogen was assigned as causative.

[a] Other infections include lung abscess, sinusitis, pharyngitis, tracheobronchitis, endocarditis, mediastinitis, myocarditis, post-operative wound infection, bone and joint infection, oral infection, eye infection, reproductive tract infection.

eTable 12. Causative pathogens of ICU-acquired infections after admission for a non-infectious condition

Gram-positive	**124 (33.9%)**	**Gram-negative**	**122 (33.3%)**
Staphylococcus aureus	30 (8.2%)	*Pseudomonas aeruginosa*	25 (6.8%)
Staphylococcus epidermidis (CNS)	29 (7.9%)	*Serratia marcescens*	18 (4.9%)
Enterococcus faecium	26 (7.1%)	*Escherichia coli*	15 (4.1%)
Enterococcus species	9 (2.2%)	*Haemophilus influenzae*	13 (3.5%)
Enterococcus faecalis	8 (2.2%)	*Enterobacter cloacae*	11 (3.0%)
Streptococcus pneumoniae	4 (1.1%)	*Klebsiella pneumoniae*	8 (2.2%)
Streptococcus species	4 (1.1%)	*Citrobacter species*	5 (1.3%)
Bacillus species	3 (0.8%)	*Proteus mirabilis*	5 (1.3%)
Streptococcus viridans	3 (0.8%)	*Stenothrophomas maltophilia*	4 (1.1%)
Clostridium difficile	2 (0.5%)	*Morganella species*	4 (1.1%)
Gram-positive cocci	2 (0.5%)	Gram-negative bacilli	4 (1.1%)
Streptococcus pyogenes	2 (0.5%)	*Klebsiella oxytoca*	3 (0.8%)
Mycobacterium tuberculosis	1 (0.3%)	*Bacteroides species*	2 (0.5%)
Streptococcus agalactiae	1 (0.3%)	*Enterobacter species*	2 (0.5%)
		Enterobacteriaceae	2 (0.5%)
		Pseudomonas species	2 (0.5%)
Virus	**2 (0.5%)**	**Fungi**	**22 (6.0%)**
Herpes simplex reactivation	1 (0.3%)	Other fungi	11 (3.0%)
Other viruses	1 (0.3%)	*Candida albicans*	4 (1.1%)
		Candida glabrata	3 (0.8%)
Other	**10 (2.7%)**	*Aspergillus species*	2 (0.5%)
		Aspergillus fumigatus	1 (0.3%)
Unknown	**137** (**37.4%)**	*Candida species*	1 (0.3%)

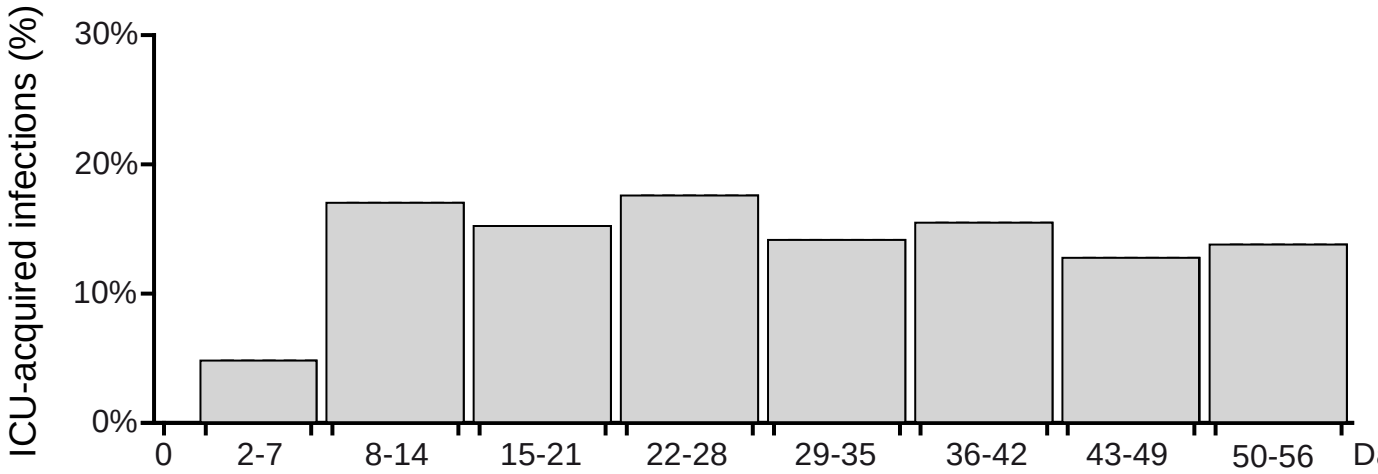
Percentages depict the portion of ICU-acquired infections (N = 366) caused by the pathogen indicated; in 41 (11.2%) of all ICU-acquired infections more than one pathogen was assigned as causative.

eTable 13. Admission diagnoses of patients admitted with a non-infectious condition stratified according to the development of an ICU-acquired infection or not

	ICU-acquired infection	No ICU-acquired infection	
Number	**291 (15.1%)**	**1630 (84.9%)**	**P value**
Cardiovascular	125 (43.0%)	670 (41.1%)	.56
Neurologic	67 (23.0%)	366 (22.5%)	.82
Respiratory	21 (7.2%)	201 (12.3%)	.01
Trauma	39 (13.4%)	176 (10.8%)	.19
Gastrointestinal	19 (6.5%)	107 (6.6%)	>.99
Transplant	15 (5.2%)	69 (4.2%)	.44
Genitourinary	0 (0%)	15 (0.9%)	.15
Metabolic	1 (0.3%)	12 (0.7%)	.71
Hematological	2 (0.7%)	7 (0.4%)	.63
Musculo-skeletal	2 (0.7%)	7 (0.4%)	.63

Abbreviations: ICU: intensive care unit.

eFigure 1. Incidence of ICU-acquired infections over time after admission for sepsis

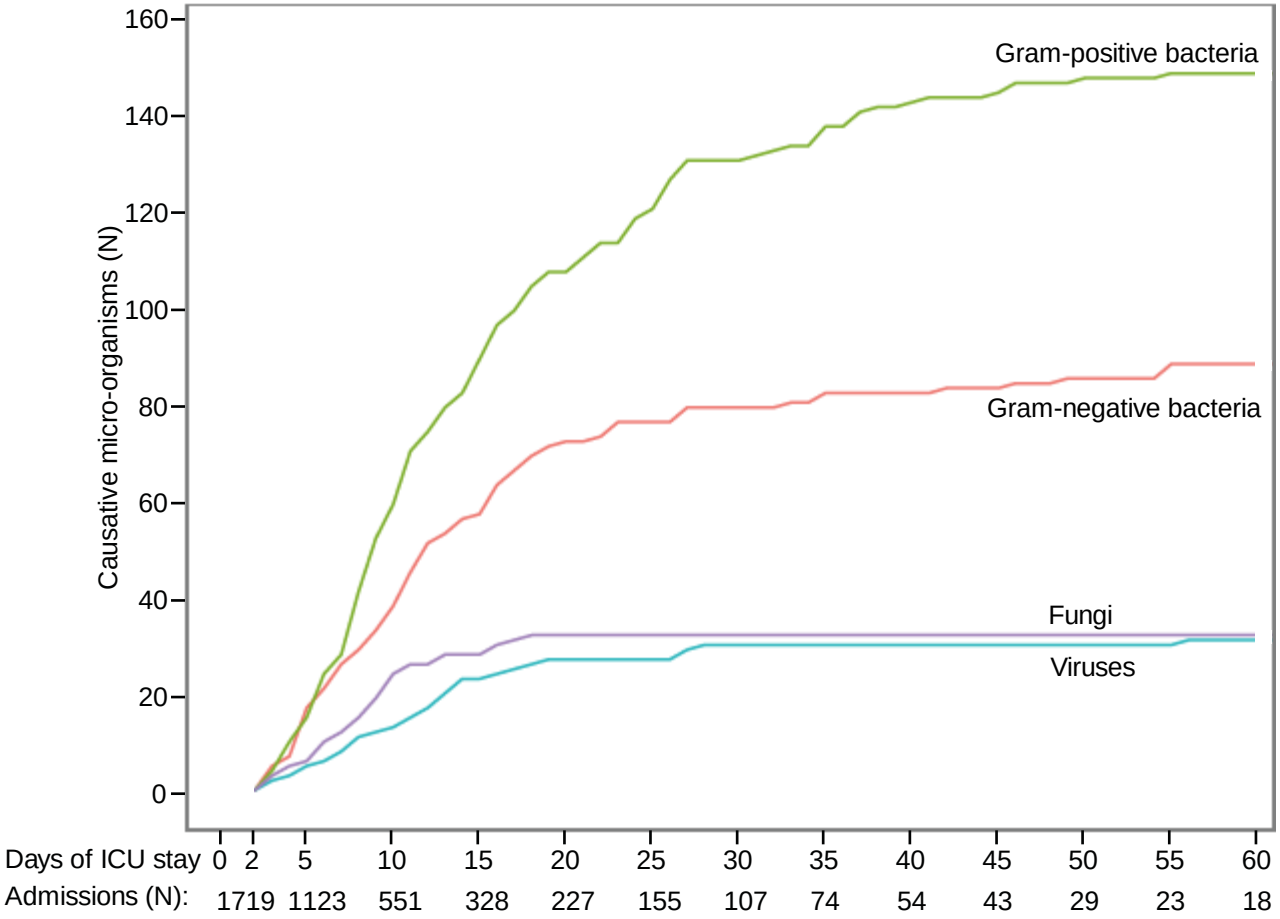


Admissions at risk at the start of the week (N):	1719	711	328	199	120	71	47	29
ICU-acquired infections per week (N):	83	121	50	35	17	11	6	4

Abbreviation: ICU: intensive care unit.

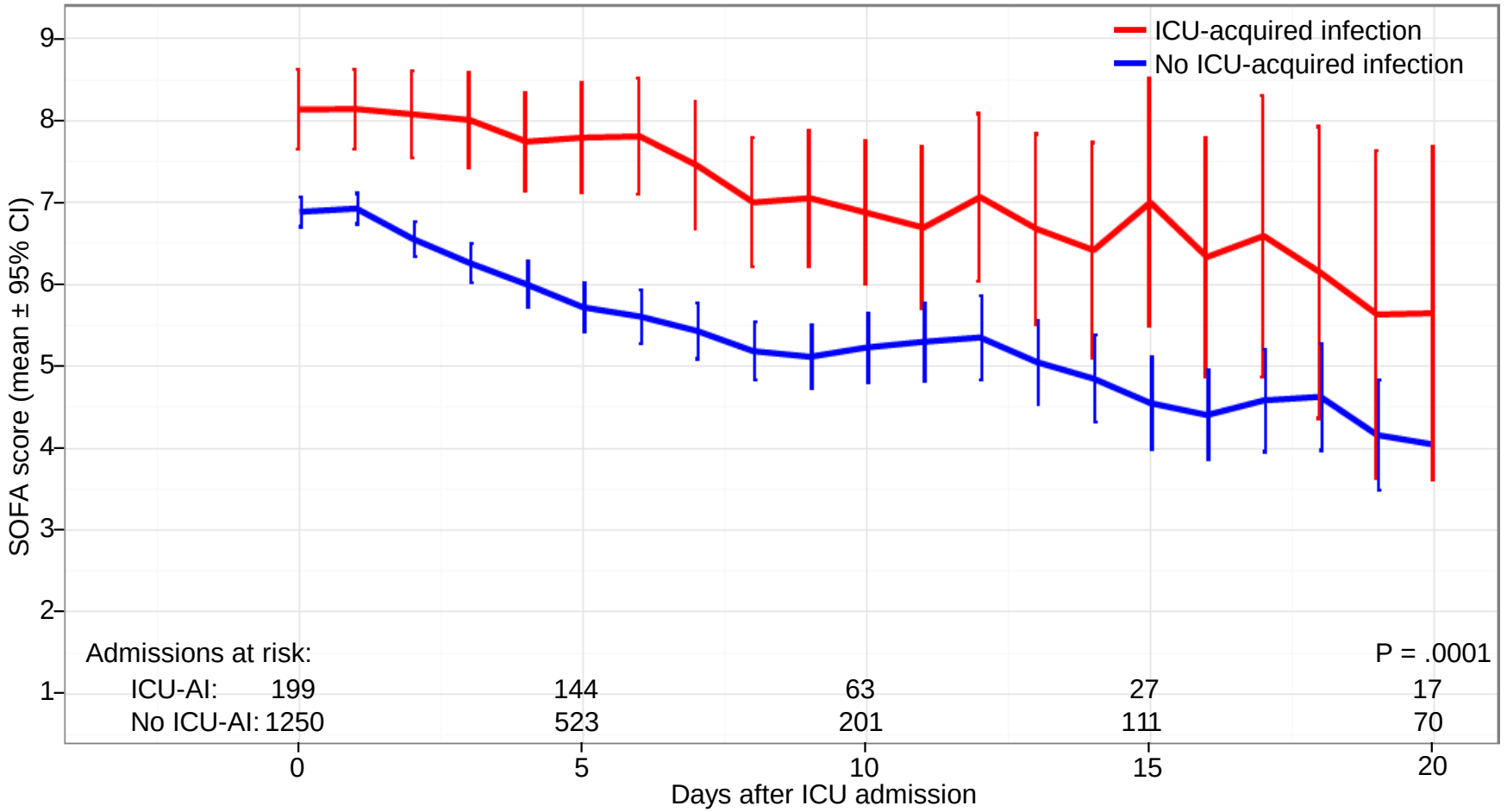
Incidence was calculated using the number of ICU-acquired infections developed in the week of interest, divided by the total number of admissions at the first day of the corresponding week.

eFigure 2. Causative micro-organisms in ICU-acquired infections after admission for sepsis



Abbreviation: ICU: intensive care unit.
Lines represent the cumulative number of causative pathogens assigned to the ICU-acquired infectious event. Since multiple pathogens could be assigned to a single infectious event, the number of pathogens exceeds the number of ICU-acquired infections. The number of patients below represent the number of patients still on the ICU at that specific day.

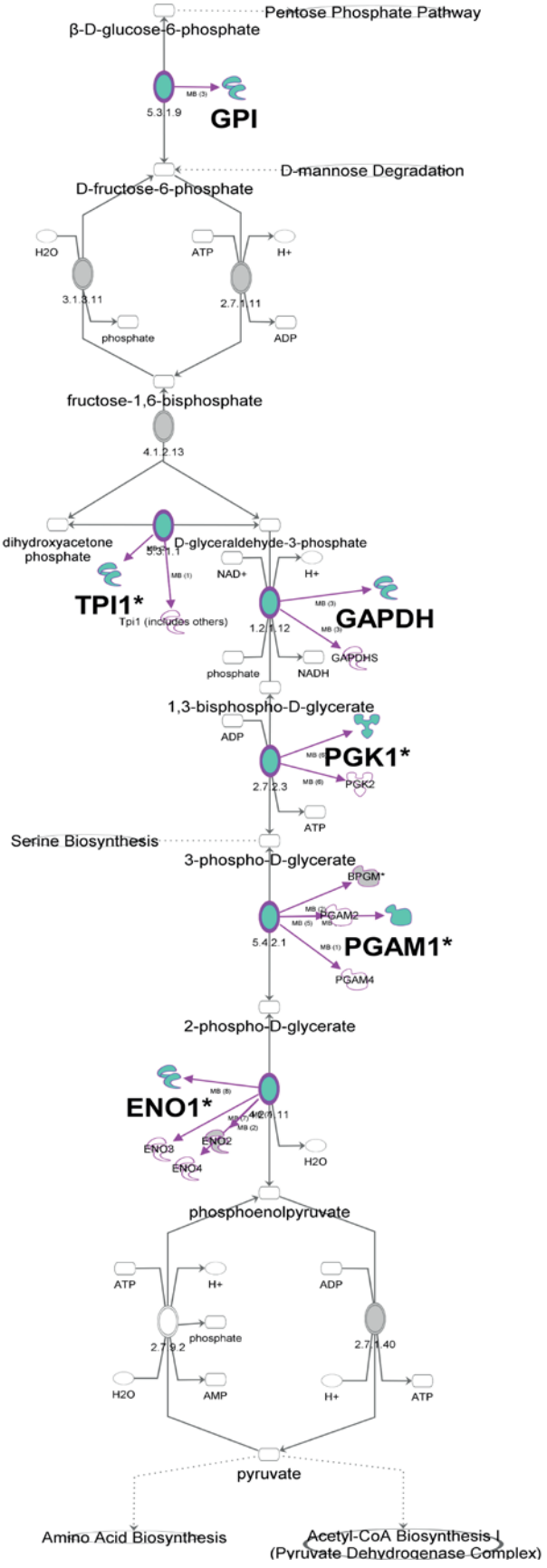
eFigure 3. SOFA scores up to 2 days before event (ICU-acquired infection or discharge/mortality) in patients admitted with sepsis stratified by development (or not) of an ICU-acquired infection



Abbreviations: ICU-AI: intensive care unit acquired infection; SOFA: sequential Organ Failure Assessment, CI: confidence interval.

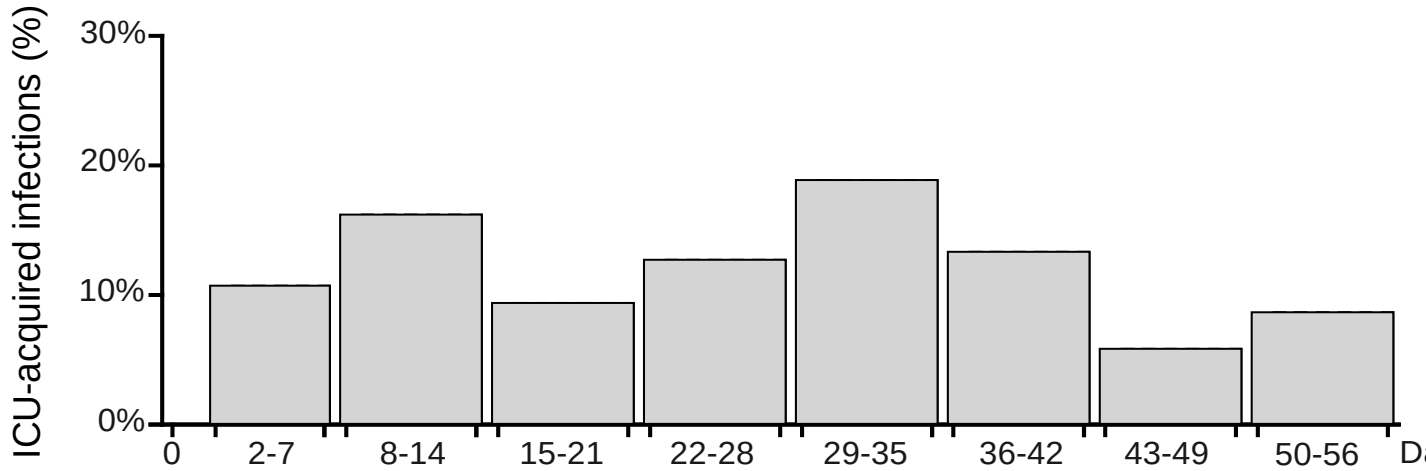
The P value represents the difference over time in SOFA scores between patients that did and those who did not develop an ICU-acquired infection (determined by mixed-effect model). This figure only includes admissions of which the SOFA score was available; for this reason the total number is lower than the total number of included admissions.

eFigure 4. Ingenuity pathway analysis showing the under-expressed glycolysis I pathway in leukocytes from patients with an ICU-acquired infection



Diagrammatic representation of the glycolysis I canonical signaling pathway. Highlighted genes (turquoise) denote significant differentially expressed genes in the paired ICU admission and follow up (ICU acquired infection) comparison. *GPI*, glucose-6-phosphate isomerase; *TPI1*, triosephosphate isomerase 1; *GAPDH*, glyceraldehyde-3-phosphate dehydrogenase; *PGK1*, phosphoglycerate kinase 1; *PGAM1*, phosphoglycerate mutase 1; *ENO1*, enolase 1. * multiple gene transcripts mapped

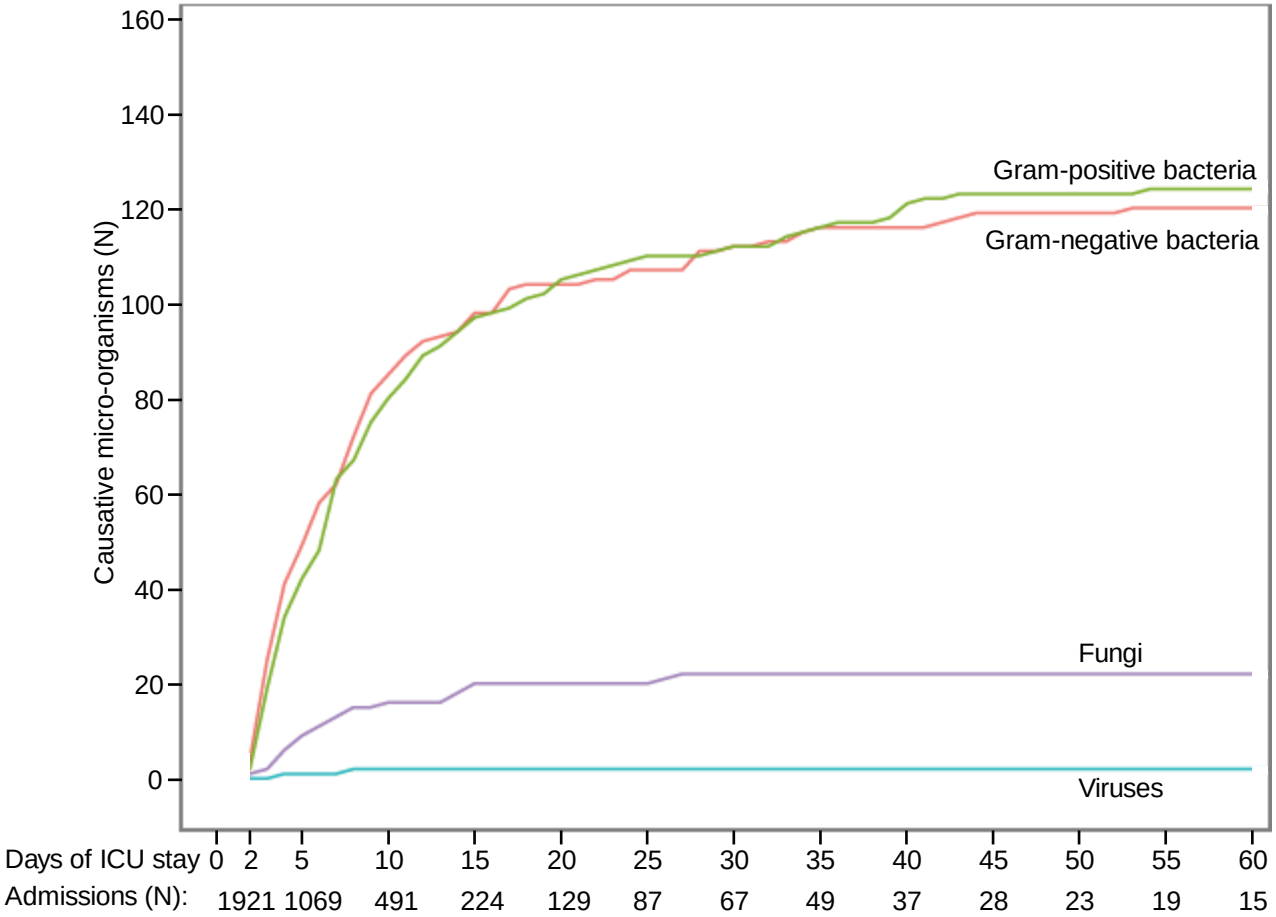
eFigure 5. Incidence of ICU-acquired infections over time after admission for non-infectious disease



Admissions at risk at the start of the week (N):	1921	605	224	110	69	45	34	23
ICU-acquired infections per week (N):	206	98	21	14	13	6	2	2

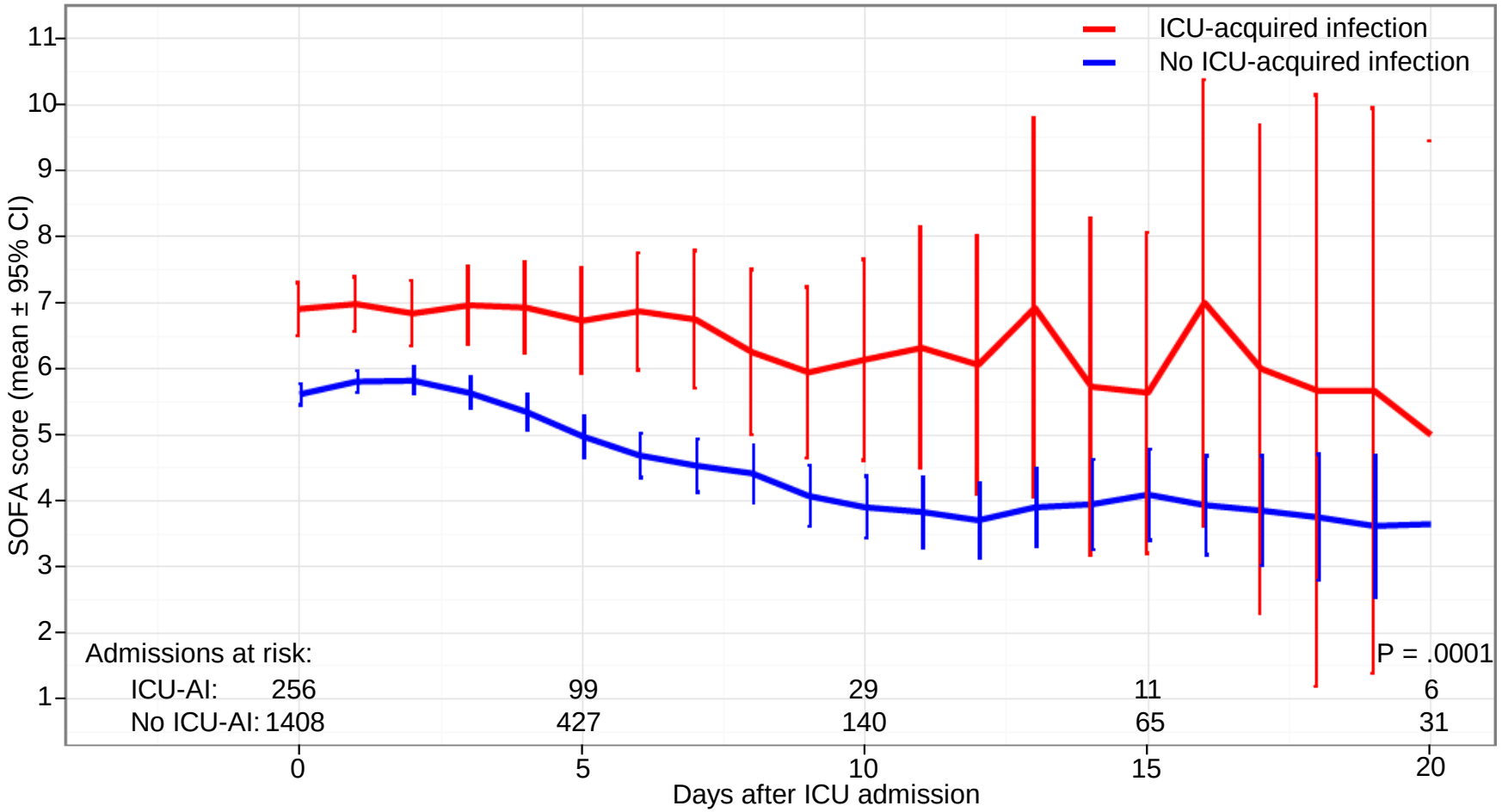
Abbreviation: ICU: intensive care unit.
Incidence was calculated using the number of ICU-acquired infections developed in the week of interest, divided by the total number of admissions at the first day of the corresponding week.

eFigure 6. Causative micro-organisms in ICU-acquired infections after admission for non-infectious disease



Abbreviations: ICU: intensive care unit.
Lines represent the cumulative number of causative pathogens assigned to the ICU-acquired infectious event. Since multiple pathogens could be assigned to a single infectious event, the number of pathogens exceeds the number of ICU-acquired infections. The number of patients below represent the number of patients still on the ICU at that specific day.

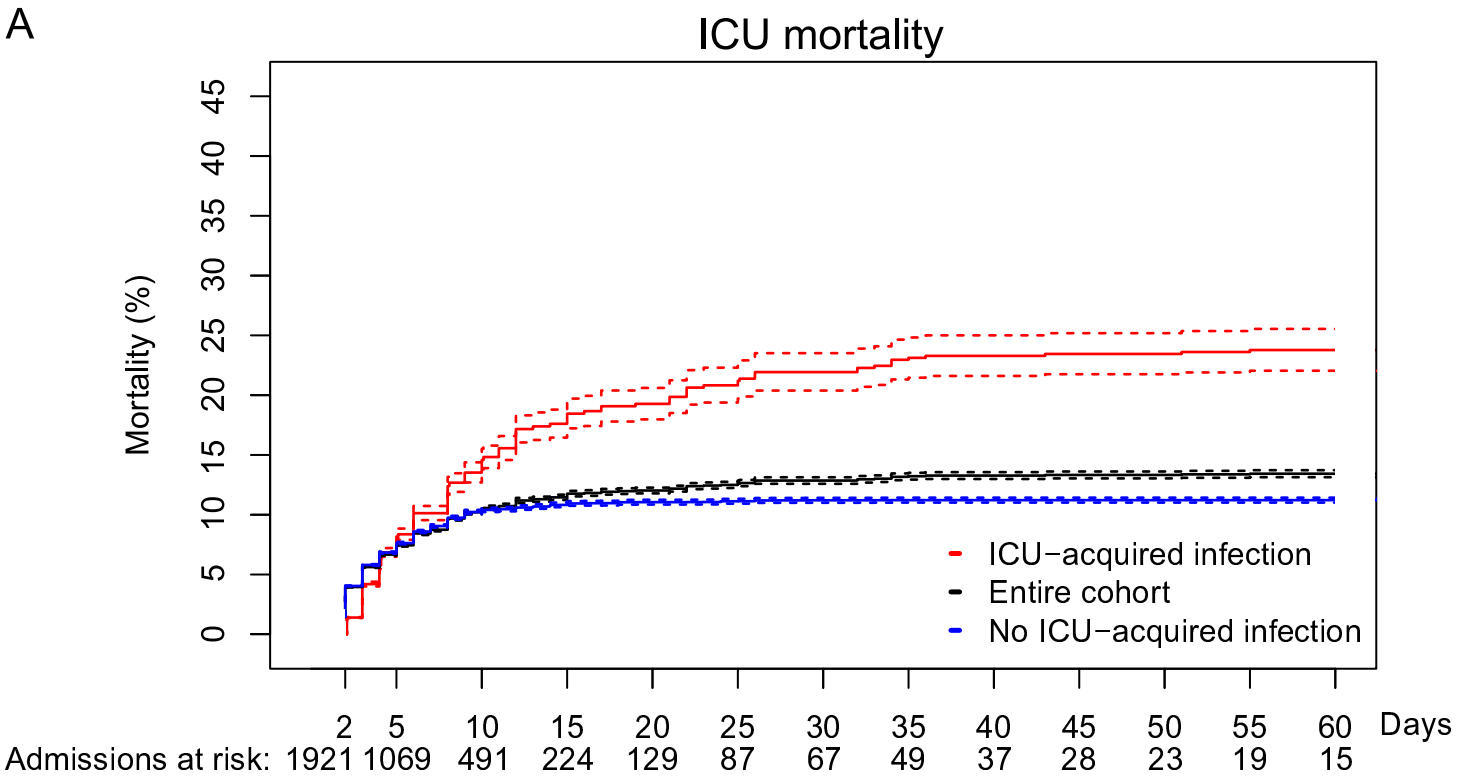
eFigure 7. SOFA scores up to 2 days before event (ICU-acquired infection of discharge/mortality) in patients admitted with a non-infectious condition stratified by development (or not) of an ICU-acquired infection

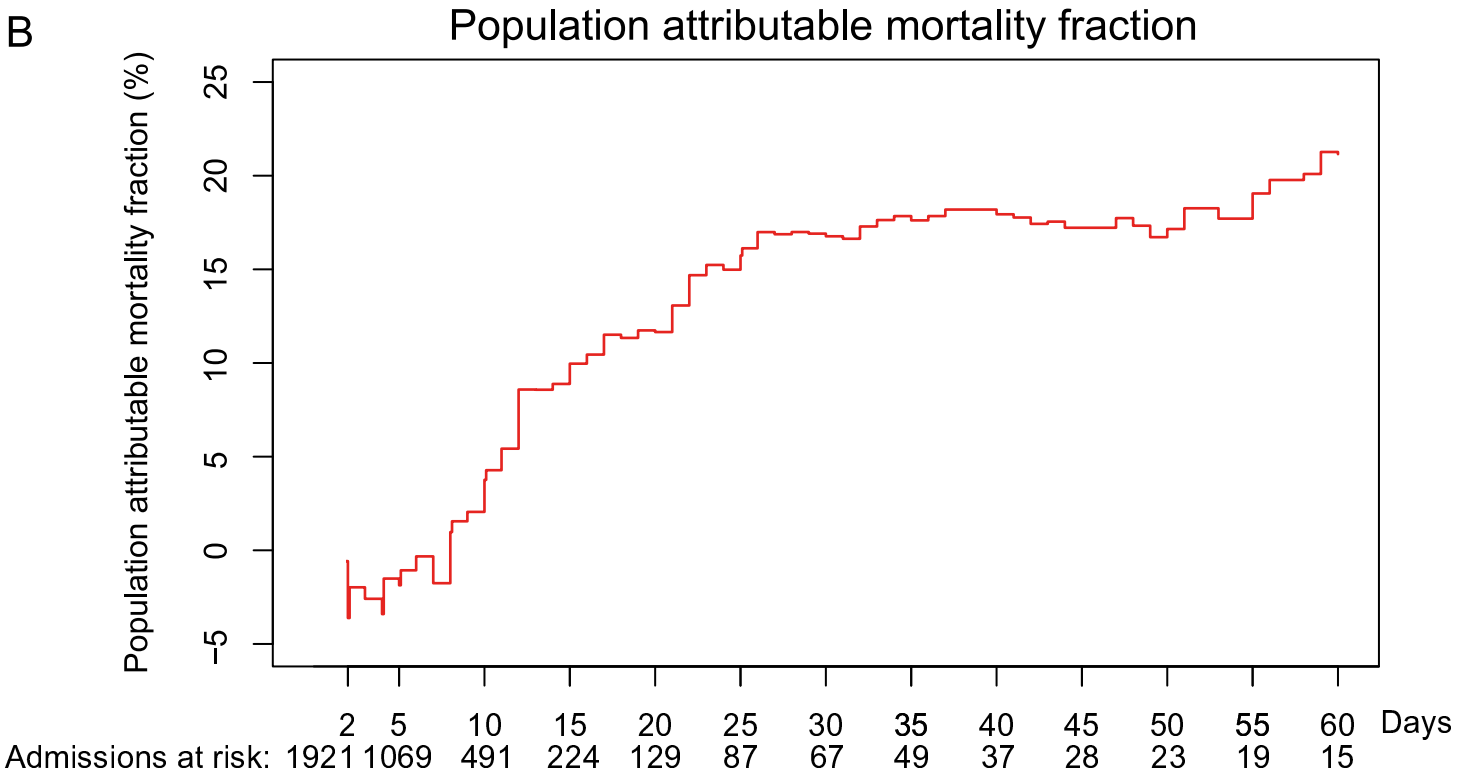


Abbreviations: ICU-AI: intensive care unit acquired infection; SOFA: sequential Organ Failure Assessment, CI: confidence interval.

The P value represents the difference over time in SOFA scores between patients that did and those who did not develop an ICU-acquired infection (determined by mixed-effect model). This figure only includes admissions of which the SOFA score was available; for this reason the total number is lower than the total number of included admissions.

eFigure 8. Population attributable mortality fraction of ICU-acquired infections in patients with a non-infectious admission diagnosis





Abbreviations: ICU: intensive care unit.

A) Estimated ICU mortality calculated using the multistate model (see Methods). The red line represents the ICU mortality in patients developing an ICU-acquired infection; the black line the ICU mortality in the entire cohort; the blue line the mortality when no ICU-acquired infections occur. Dashed lines represent 95% confidence intervals.

B) Population attributable intensive care unit mortality fraction over time adjusted for quartiles of Acute Physiology and Chronic Health Evaluation IV score and quartiles of age. The population attributable mortality fraction was expressed as the percentage of ICU mortality caused by the ICU-acquired infections. The negative values of attributable mortality fraction in the first 7 days after ICU admission are most likely driven by the most severely ill patients encountering the competing event (death without ICU-acquired infection) before being able to develop an ICU-acquired infection.(15)

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