

Sepsis sévère

M. Wolff

Hôpital Bichat-Claude Bernard

UFR Paris Diderot, EA 3964, Paris 7.



2011



Systemic inflammatory response syndrome

Two or more of the following:

- Body temperature $>38.5^{\circ}\text{C}$ or $<35.0^{\circ}\text{C}$
- Heart rate >90 beats per minute
- Respiratory rate >20 breaths per minute or arterial CO_2 tension <32 mm Hg or need for mechanical ventilation
- White blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or immature forms $>10\%$

Sepsis

Systemic inflammatory response syndrome and documented infection (culture or gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection—eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)

Sepsis sévère

Sepsis and at least one sign of organ hypoperfusion or organ dysfunction:

- Areas of mottled skin
- Capillary refilling time ≥ 3 s
- Urinary output < 0.5 mL/kg for at least 1 h or renal replacement therapy
- Lactates > 2 mmol/L
- Abrupt change in mental status or abnormal electroencephalogram
- Platelet counts $< 100\ 000$ /mL or disseminated intravascular coagulation
- Acute lung injury—acute respiratory distress syndrome
- Cardiac dysfunction (echocardiography)

Septic shock

Severe sepsis and one of:

- Systemic mean blood pressure <60 mm Hg (<80 mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg
- Need for dopamine >5 $\mu\text{g}/\text{kg}$ per min or norepinephrine or epinephrine <0.25 $\mu\text{g}/\text{kg}$ per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Refractory septic shock

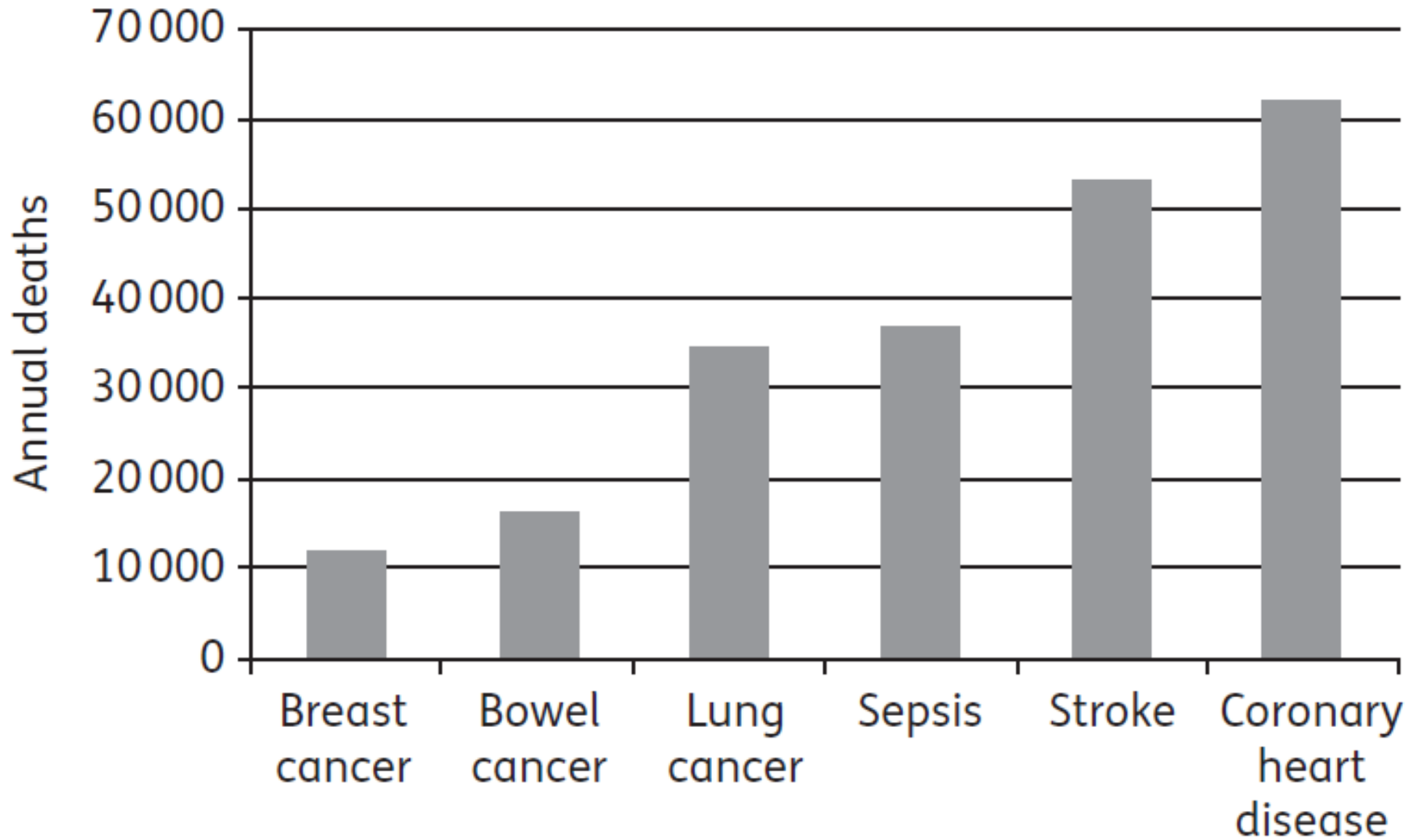
Need for dopamine >15 $\mu\text{g}/\text{kg}$ per min or norepinephrine or epinephrine >0.25 $\mu\text{g}/\text{kg}$ per min to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

Incidence

- Sepsis requérant l'admission en réanimation: 0.25-0.38 pour 1000 personnes/an soit environ 2 millions d'admissions/an

Ron Daniels JAC 2011

Mortalité



Ron Daniels JAC 2011

Current Epidemiology of Septic Shock

The CUB-Réa Network

Djillali Annane, Philippe Aegerter, Marie Claude Jars-Guincestre, and Bertrand Guidet
for the CUB-Réa Network

Service de Réanimation Médicale, Hôpital Raymond Poincaré, Assistance Publique Hôpitaux de Paris, Garches; Service de Biostatistique et Informatique Médicale, Hôpital Ambroise Paré, Assistance Publique Hôpitaux de Paris, Boulogne; Service de Réanimation Médicale, Hôpital Saint Antoine, Assistance Publique Hôpitaux de Paris, Paris; and INSERM U444, Paris, France.

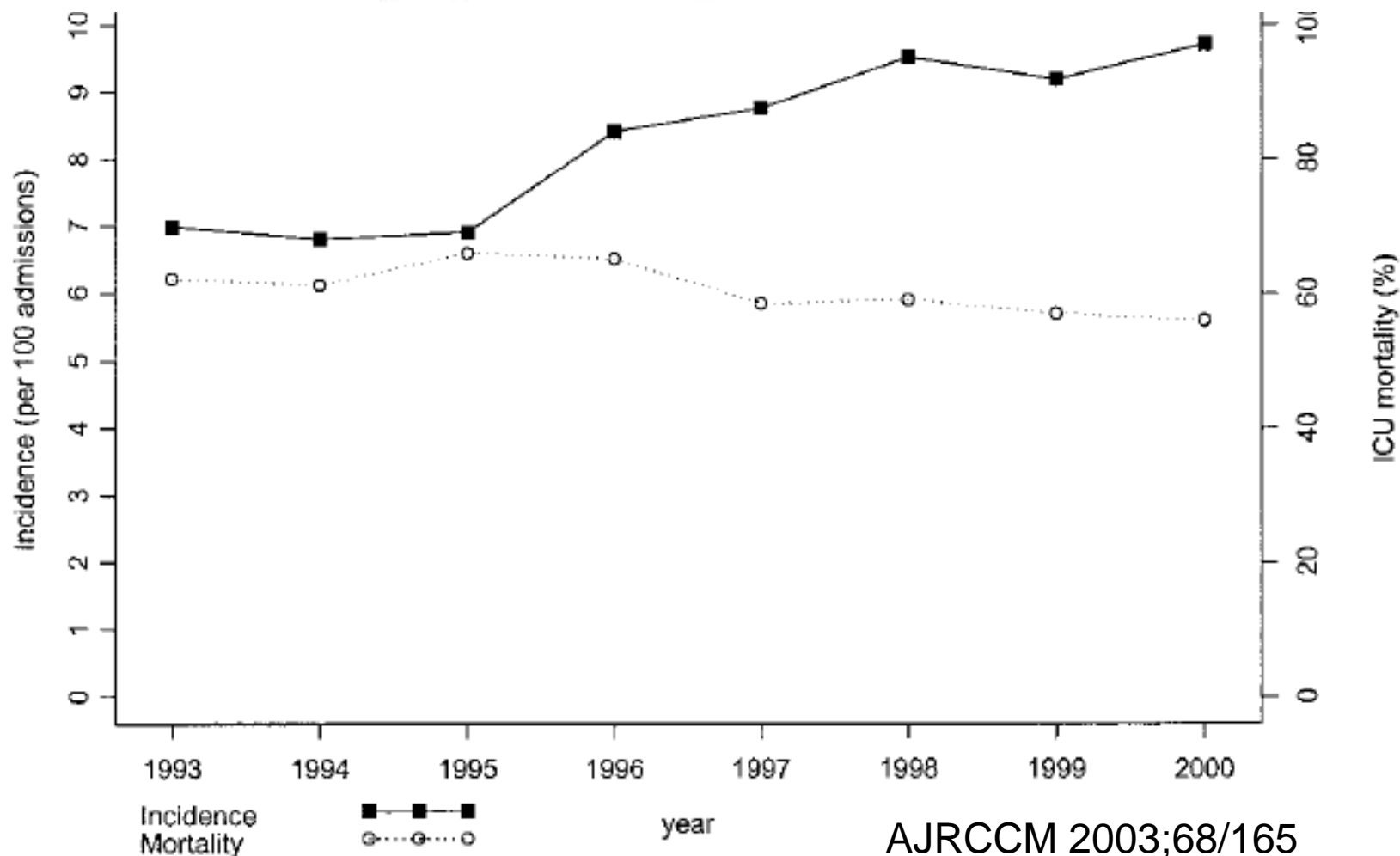


TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF 8,251 INTENSIVE CARE UNIT STAYS WITH SEPTIC SHOCK FROM 1993 TO 2000

Variables	Septic Shock (<i>n</i> = 8,251)	Population without Septic Shock (<i>n</i> = 92,293)	<i>p</i> Value*
Baseline descriptors			
Age, yr	61.4 ± 16.6	53.9 ± 19.5	<i>p</i> < 0.001
Sex, female	36.7 (35.6–37.7)	42.0 (41.6–42.3)	<i>p</i> < 0.001
Admission category, medical	78.2 (77.3–79.1)	87.7 (87.5–87.9)	<i>p</i> < 0.001
Type of admission, direct	36.7 (35.7–37.7)	58.1 (57.8–58.4)	<i>p</i> < 0.001
Reason for admission, shock	33.7 (32.7–34.8)	6.5 (6.3–6.6)	<i>p</i> < 0.001
Reason for admission, infection	35.4 (34.3–36.4)	7.6 (7.5–7.8)	<i>p</i> < 0.001
McCabe > 0	47.2 (46.1–48.2)	28.1 (27.8–28.4)	<i>p</i> < 0.001
Comorbidity			
Immune deficiency	21.9 (21.0–22.7)	11.4 (11.2–11.6)	<i>p</i> < 0.001
Diabetes mellitus	2.2 (1.9–2.5)	2.8 (2.7–2.9)	<i>p</i> = 0.002
Chronic renal failure	3.2 (2.9–3.6)	3.7 (3.5–3.8)	<i>p</i> = 0.05
Hematologic malignancy	8.4 (7.8–9.0)	2.5 (2.4–2.6)	<i>p</i> < 0.001
Cancer	6.9 (6.3–7.4)	3.7 (3.6–3.8)	<i>p</i> < 0.001
HIV-related disease	5.8 (5.3–6.3)	3.3 (3.1–3.4)	<i>p</i> < 0.001
Chronic pulmonary disease	9.2 (8.6–9.8)	13.5 (13.3–13.7)	<i>p</i> < 0.001
SAPS II	58.3 ± 23.9	34.4 ± 20.32	<i>p</i> < 0.001
ALI-ARDS	22.2 (21.3–23.1)	3.0 (2.9–3.1)	<i>p</i> < 0.001

**Preintervention
Cohort (n = 854)**

Mortality, No. (%) [95% CI]	
Hospital	376 (44.0) [41-47]
28-d	311 (36.4) [33-40]
ICU	315 (36.9) [34-40]
Hospital stay, d ^a	
Mean (SD) [95% CI]	28.7 (23.4) [26.6-30.8]
Median (IQR)	20.9 (13.5-35.7)
ICU stay, d ^a	
Mean (SD) [95% CI]	13.4 (16.0) [11.9-14.0]
Median (IQR)	7.6 (4.5-15.0)

Ferrer R et al JAMA 2008

Characteristics of Sepsis Patients (n = 1177)

Country	No. of Centers	No. of Patients (%)	ICU Mortality, n (%) ^a	Hospital Mortality, n (%) ^a	Frequency, n (%)	SAPS II Score, Mean ± SD	ICU Mortality, n (%) ^a	Hospital Mortality, n (%) ^a	Severe Sepsis, n (%)
Austria	8	68 (2)	14 (21)	16 (24) ^b	26 (38)	42.5 ± 17.2	6 (23)	8 (31)	18 (27)
Belgium	19	703 (22)	86 (12)	120 (17)	188 (27)	38.7 ± 15.0	39 (21)	57 (31) ^c	125 (18)
Eastern Europe ^d	15	174 (6)	41 (24)	53 (31) ^b	83 (48)	40.2 ± 15.0	24 (29)	31 (37)	74 (43)
France	21	332 (11)	63 (19)	70 (21)	136 (41)	43.4 ± 18.0	37 (27)	44 (32)	99 (30)
Germany	21	329 (11)	39 (12)	51 (16) ^e	102 (31)	41.6 ± 15.8	16 (16)	20 (20)	78 (24)
Greece	10	109 (4)	18 (17)	23 (21)	47 (43)	47.1 ± 20.2	14 (30)	16 (34)	41 (38)
Italy	24	237 (8)	61 (26)	73 (31) ^e	89 (38)	43.4 ± 15.3	31 (35)	39 (45) ^c	75 (32)
Netherlands	7	144 (5)	33 (23)	43 (31)	56 (39)	43.8 ± 16.8	18 (32)	25 (47) ^c	49 (34)
Portugal	6	69 (2)	24 (35)	28 (41)	50 (73)	46.2 ± 14.8	16 (32)	19 (38)	44 (64)
Scandinavia ^f	16	209 (7)	29 (14)	51 (24)	74 (35)	41.1 ± 15.7	14 (19)	45 (39)	52 (25)
Spain	13	202 (6)	44 (22) ^g	49 (26) ^h	70 (35)	38.3 ± 17.0	21 (30)	26 (38) ^b	57 (28)
Switzerland	4	114 (4)	9 (8)	16 (14)	20 (18)	38.4 ± 15.4	2 (10)	4 (20)	11 (10)
UK and Ireland	34	457 (15)	122 (27)	154 (34)	236 (52)	42.6 ± 17.6	75 (32)	95 (41)	207 (45)
Total	198	3147	583 (19) ^g	747 (24)	1177 (37)	42.3 ± 16.6	313 (27)	413 (36) ⁱ	930 (30)

Total	1177 (37)	42.3 ± 16.6	313 (27)	413 (36) ⁱ	930 (30)
--------------	-----------	-------------	----------	-----------------------	----------

MORTALITE ATTRIBUTABLE

Measure of association		95% CI
Matched Excess Risk (%)	26.7	24.9 - 28.6
Matched Risk Ratio	2.00	1.91 - 2.10
Matched Odds Ratio	4.08	4.05 - 4.11
OR, adjusted for all prognostic variables	2.39	2.08 - 2.76

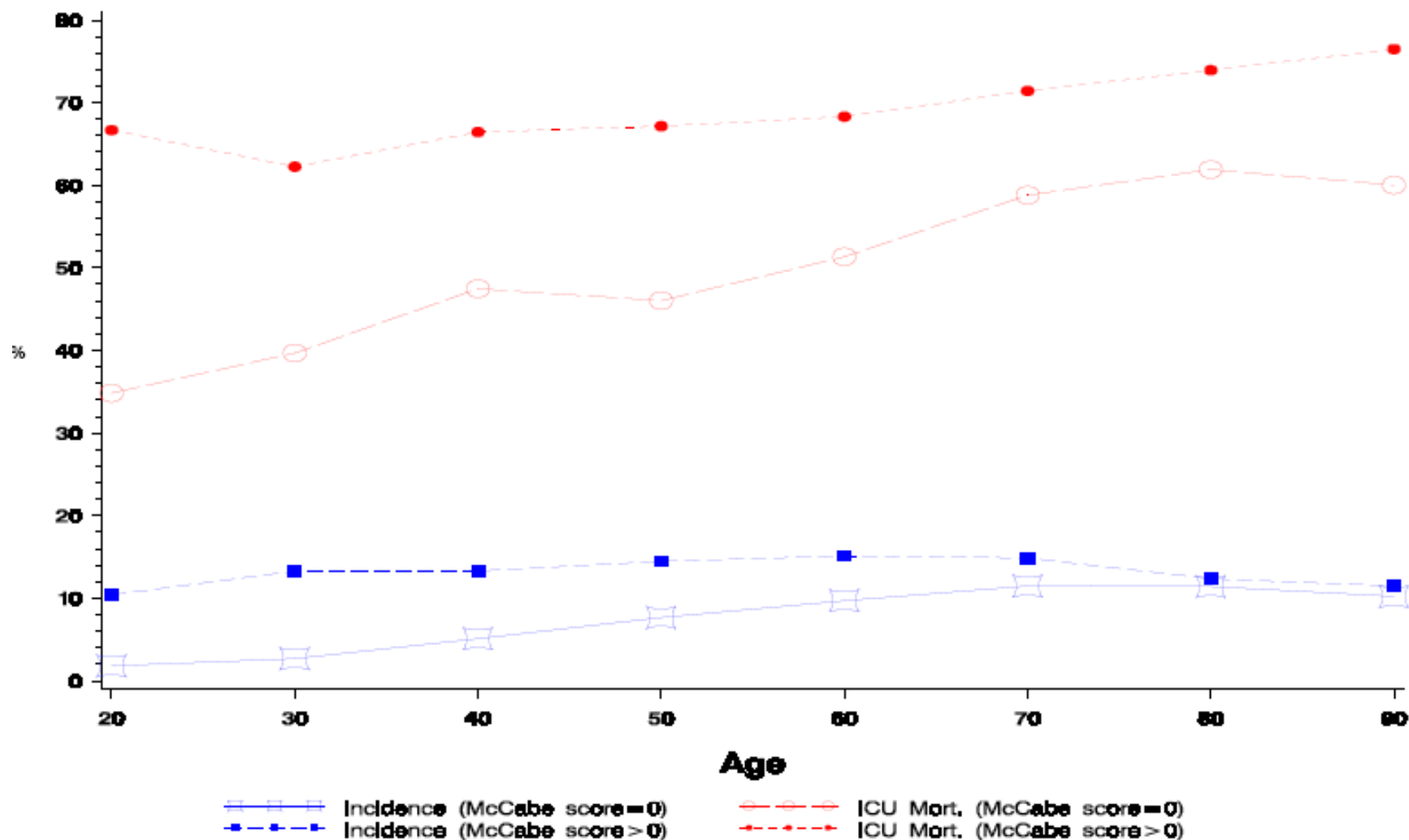
Facteurs associés à la mortalité

- ❑ Age, facteurs génétiques
- ❑ Co-morbidités
- ❑ Site de l'infection (urines moins grave)
- ❑ Pathogènes en cause
- ❑ Nombre de défaillances viscérales
- ❑ Retard à l'antibiothérapie
- ❑ Non optimisation du traitement symptomatique

TABLE 2. FACTORS THAT AFFECT INTENSIVE CARE UNIT SURVIVAL IN 8,251 INTENSIVE CARE UNIT STAYS WITH SEPTIC SHOCK OVER THE 8-YEAR PERIOD 1993–2000: MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

Variables	Odds Ratio	95% Confidence Interval	p Value
Period, 1997–2000	0.61	0.55–0.68	$< 10^{-4}$
Demographic characteristics			
Age, by 10 yr	1.23	1.18–1.29	$< 10^{-4}$
McCabe > 0	4.01	2.70–5.94	$< 10^{-4}$
Admission category, medical	1.75	1.53–2.01	$< 10^{-4}$
Type of admission, direct	0.84	0.75–0.95	$< 10^{-2}$
Severity of illness			
SAPS II	1.07	1.05–1.09	$< 10^{-4}$
$\ln(1 + \text{SAPS II})$	0.16	0.07–0.40	$< 10^{-4}$
Interaction term: age \times (McCabe > 0)	0.89	0.83–0.95	$< 10^{-3}$
ALI-ARDS	1.70	1.47–1.97	$< 10^{-4}$
Acute renal failure	1.43	1.28–1.61	$< 10^{-4}$
Characteristics of infection			
Unknown site of infection	1.28	1.12–1.47	$< 10^{-3}$
Positive bacterial strains	0.74	0.66–0.83	$< 10^{-4}$
Fungus	1.81	1.36–2.41	$< 10^{-4}$
Interventions			
Mechanical ventilation	4.72	4.10–5.42	$< 10^{-4}$
Vasopressors*	1.52	1.28–21.80	$< 10^{-4}$
Renal support	2.03	1.77–2.32	$< 10^{-4}$

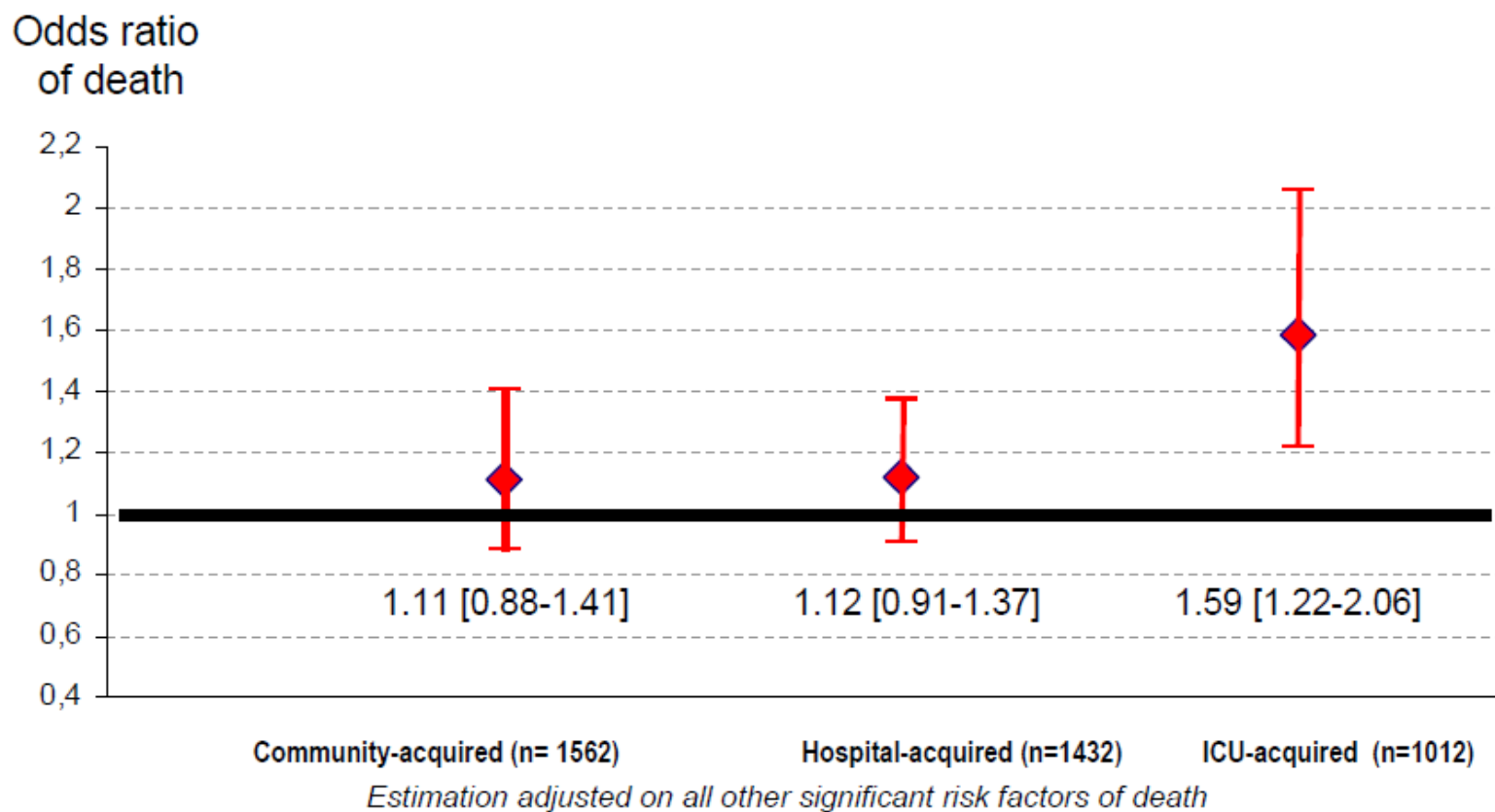
CO-MORBIDITE

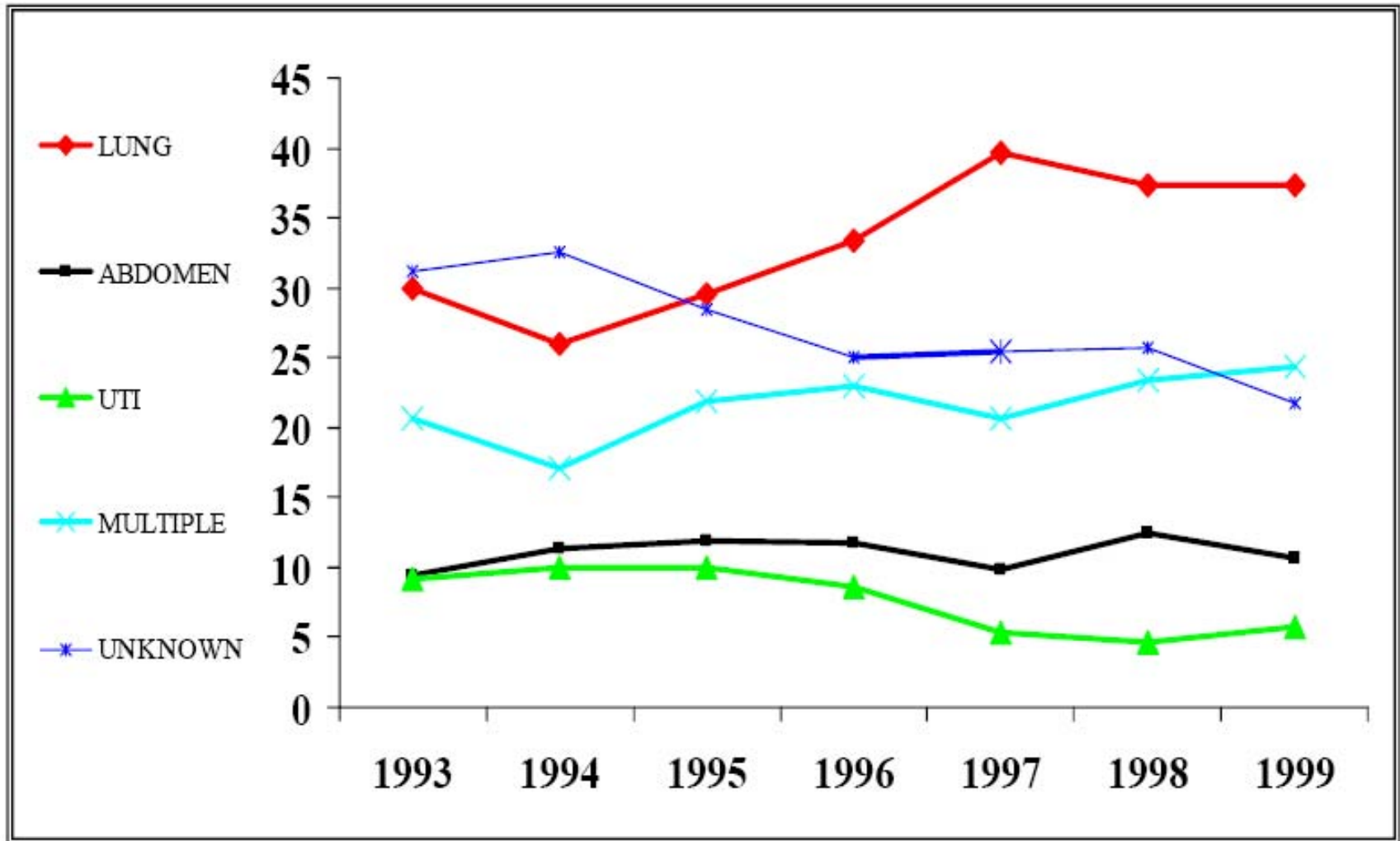


Genetic Polymorphisms and Severe Sepsis

Gene	Susceptibility and/or Outcome
Mannose Binding Lectin SP-B	Meningococemia, Severe Sepsis, CAP CAP
Toll-Like Receptors CD14	Septic Shock, Legionnaire's Disease, CAP Septic Shock, CAP
IRAK-1; TIRAP; I κ B α FC γ RII Receptor	Severe Sepsis, Pneumococemia, CAP Meningococemia; Pneumococemia, CAP
TNF locus	Meningococemia; Septic Shock, CAP
IL-18; IL-1 locus	Severe Sepsis
IL-10	Severe Sepsis, Meningococemia, CAP
IL-6	Severe sepsis, CAP
IL-4	Viral Pneumonia
ACE	Severe Sepsis
Caspase 12	Severe Sepsis
PAI-1	Meningococemia; Severe sepsis, CAP
Factor V Leiden	Meningococemia; Severe sepsis
Protein C; Fibrinogen	Severe Sepsis

Impact of bacteremia according to the date of severe sepsis

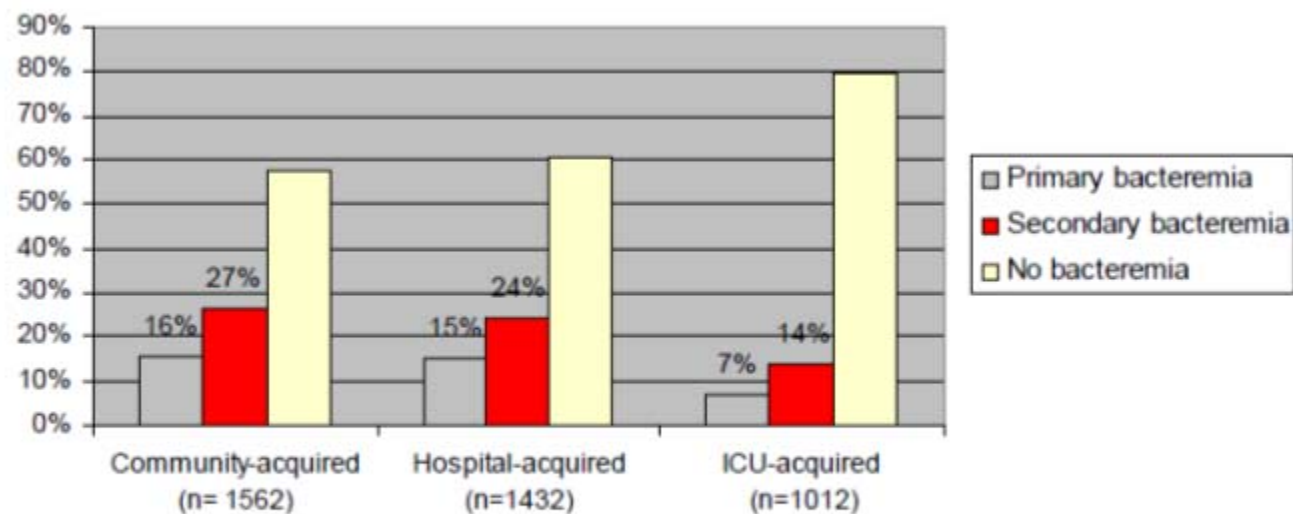
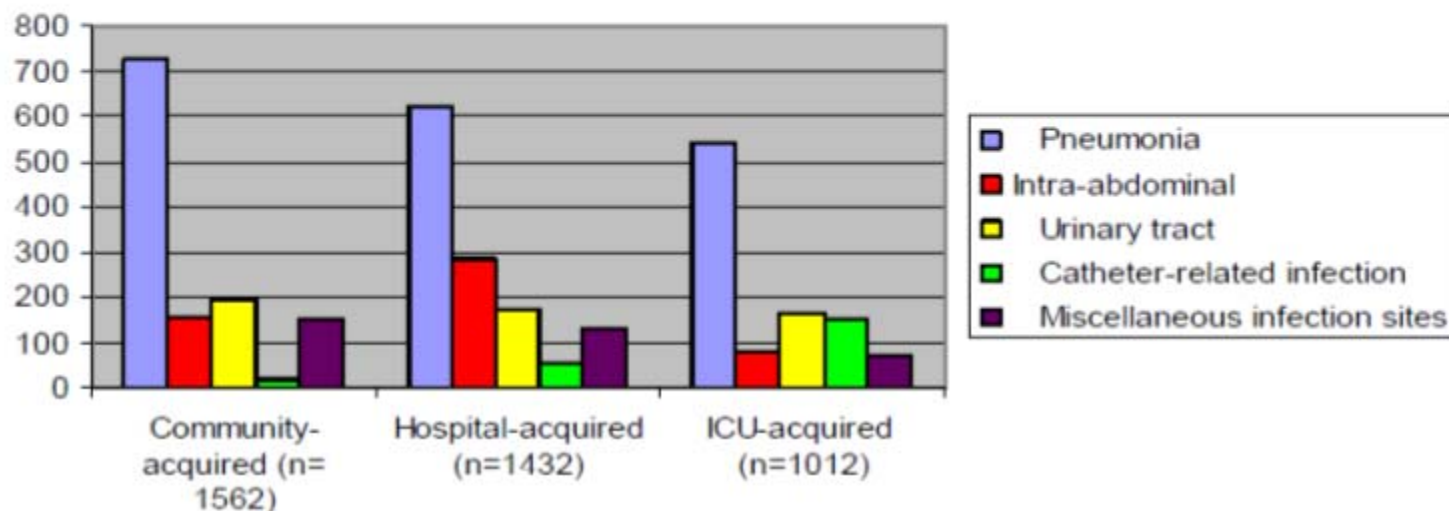


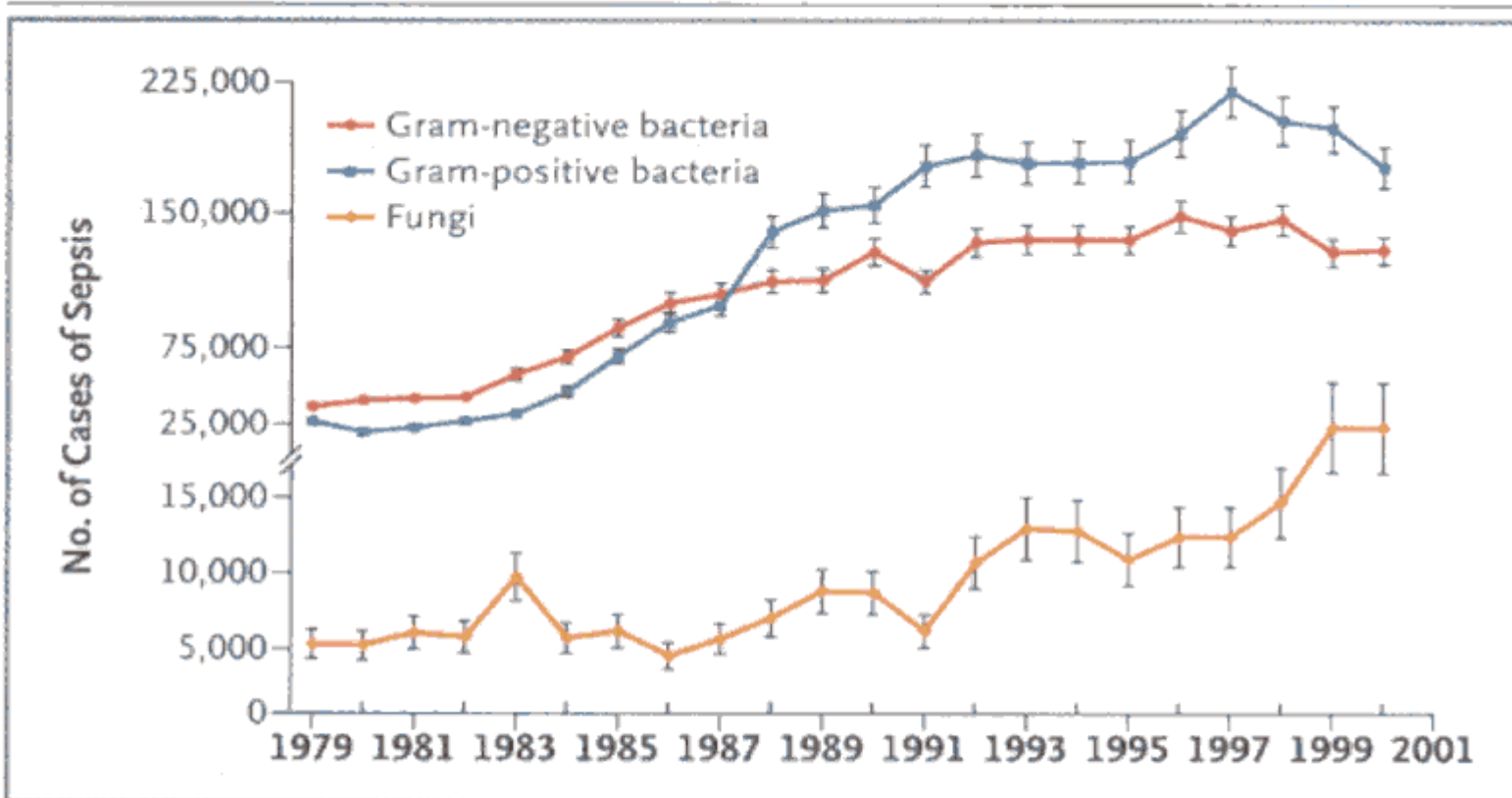


Annane, AJRCCM 2003

Sources of severe sepsis and bacteremia in ICU

sources of severe sepsis





Epidémiologie microbienne des états septiques aux Etats-Unis entre 1999 et 2001.

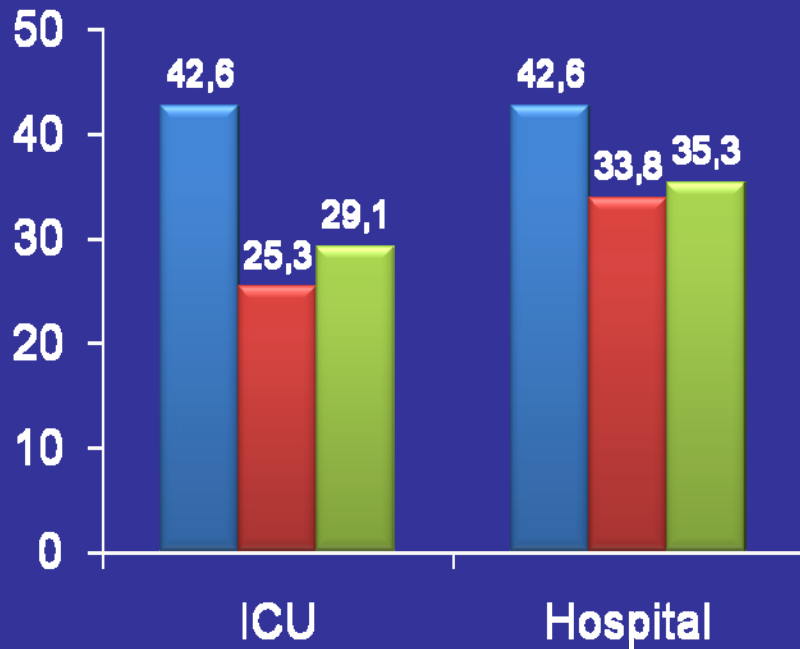
	Estimated frequency*
Gram-positive bacteria	30–50%
Meticillin-susceptible <i>S aureus</i>	14–24%
Meticillin-resistant <i>S aureus</i>	5–11%
Other <i>Staphylococcus</i> spp	1–3%
<i>Streptococcus pneumoniae</i>	9–12%
Other <i>Streptococcus</i> spp	6–11%
<i>Enterococcus</i> spp	3–13%
Anaerobes	1–2%
Other gram-positive bacteria	1–5%

Gram-negative bacteria	25–30%
<i>E coli</i>	9–27%
<i>Pseudomonas aeruginosa</i>	8–15%
<i>Klebsiella pneumoniae</i>	2–7%
Other <i>Enterobacter</i> spp	6–16%
<i>Haemophilus influenzae</i>	2–10%
Anaerobes	3–7%
Other gram-negative bacteria	3–12%
Fungus	
<i>Candida albicans</i>	1–3%
Other <i>Candida</i> spp	1–2%
Yeast	1%
Parasites	1–3%
Viruses	2–4%

Impact of BSI on mortality and length of stay (EPIC II)

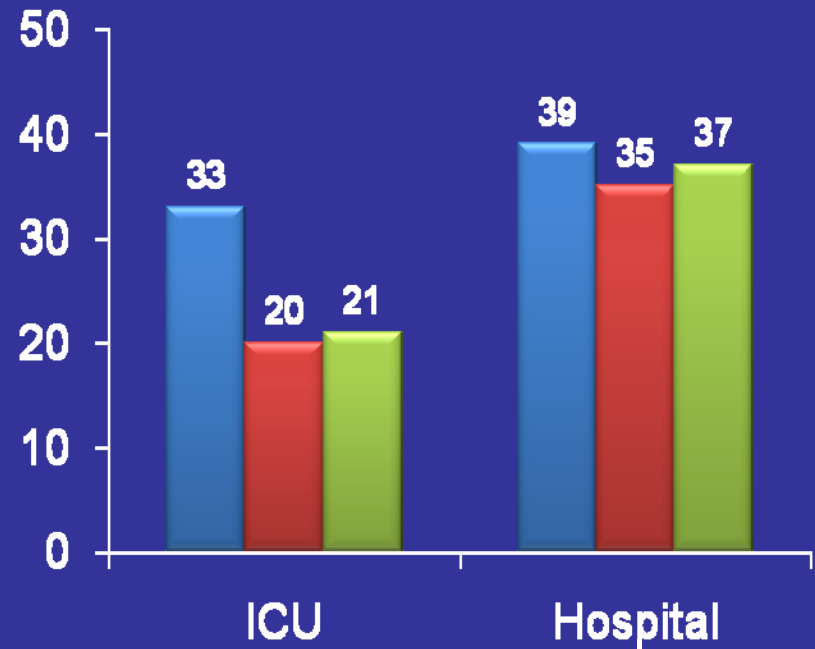
Mortality (%)

■ **Candida** (n=61) ■ **Gram +** (n=420) ■ **Gram -** (n=264)



Length of stay (days)

■ **Candida** (n=61) ■ **Gram +** (n=420) ■ **Gram -** (n=264)



Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock*

Anand Kumar, MD; Daniel Roberts, MD; Kenneth E. Wood, DO; Bruce Light, MD; Joseph E. Parrillo, MD; Satendra Sharma, MD; Robert Suppes, BSc; Daniel Feinstein, MD; Sergio Zanotti, MD; Leo Taiberg, MD; David Gurka, MD; Aseem Kumar, PhD; Mary Cheang, MSc

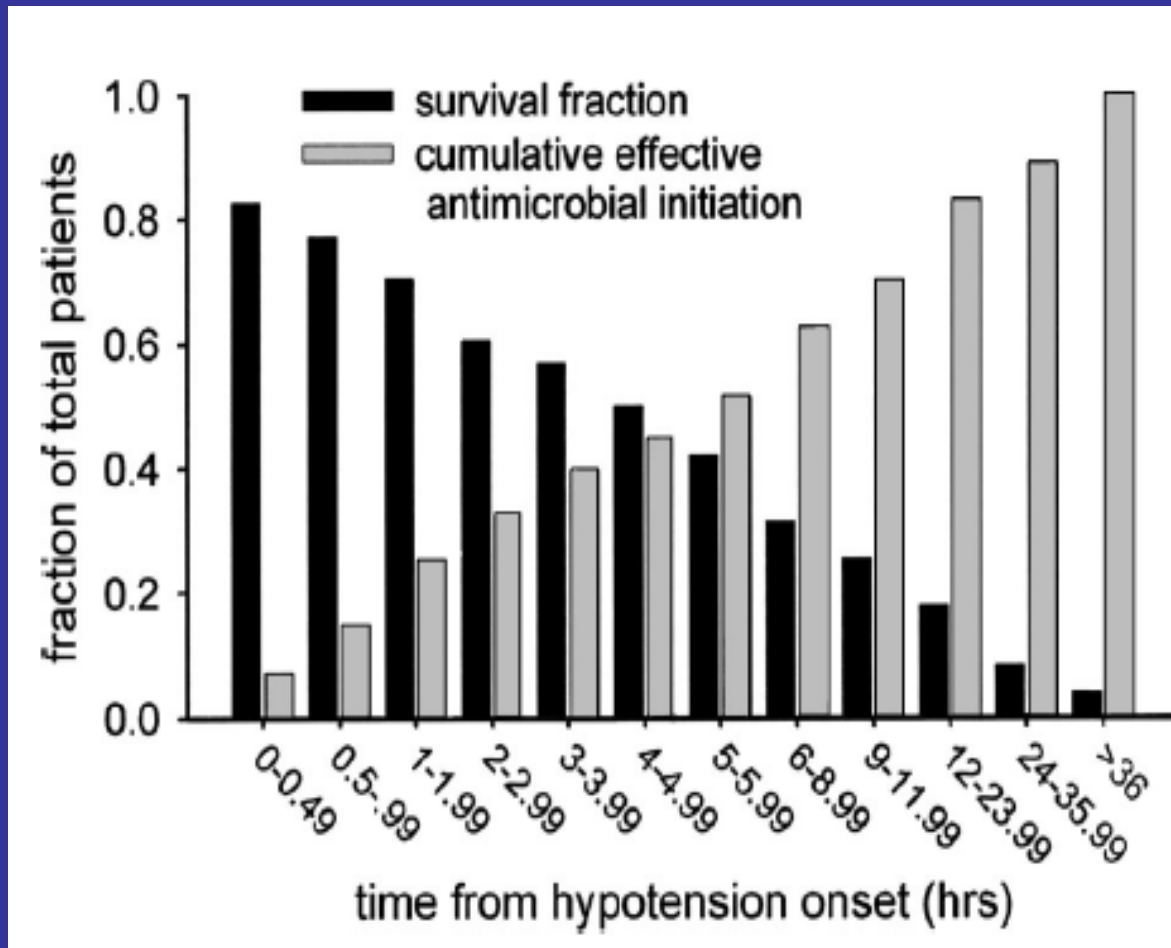


Table 4. Multivariate Analysis of Factors Associated With Mortality

Factor	Odd Ratio (95% CI)	<i>P</i> Value
Interventional cohort	0.81 (0.67-0.98)	.03
Age ^a	1.014 (1.008-1.020)	<.001
APACHE II ^b	1.10 (1.08-1.11)	<.001
Sepsis presentation and diagnosis ^c		
Medical- surgical ward	1.63 (1.34-1.99)	<.001
ICU	2.39 (1.81-3.15)	<.001
Shock	1.28 (1.01-1.62)	.04

Evaluation épidémiologique de la gravité

1. Scores de gravité à l'admission en réanimation:
IGS2 (SAPS 2, Apache 2 ou 3)
2. Scores de défaillance viscérale
 - SOFA
 - LODS
 - ODIN
 - etc...

A quoi servent ces scores ?

- ❑ Pas à établir un pronostic individuel
- ❑ Mais plutôt à comparer des populations
 - ❑ Comparaison des services de réanimation sur la gravité des patients
 - ❑ Comparaison mortalité prédite-mortalité observée
 - ❑ Etudes épidémiologiques, interventionnelles en réanimation

SAPS II (expanded)

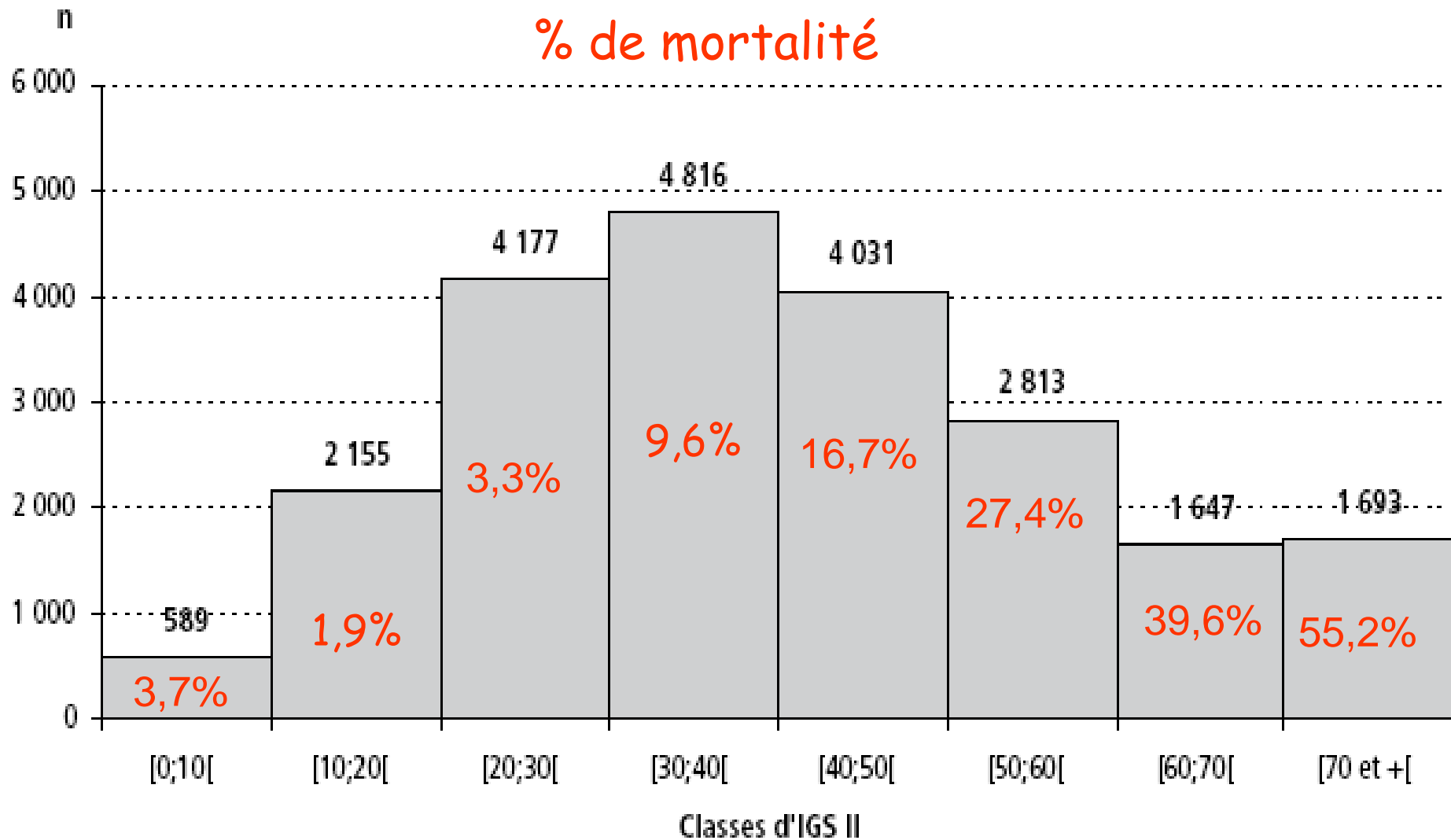
Mode d'admission <input type="text"/> 0	Maladies chroniques <input type="text"/> 0	Score de Glasgow <input type="text"/> 0
Age <input type="text"/> 0	P. Art. Syst. <input type="text"/> 0	Fréq.Cardiaque <input type="text"/> 0
Température <input type="text"/> 0	PaO2/FIO2(mmHg) Si VM ou CPAP <input type="text"/> 0	Diurèse (L/24 H) <input type="text"/> 0
Urée sanguine <input type="text"/> 0	Leucocytes <input type="text"/> 0	Kaliémie <input type="text"/> 0
Natrémie <input type="text"/> 0	HCO3- <input type="text"/> 0	Bilirubine (si ictère) <input type="text"/> 0

(les paramètres sont colligés dans les 24 H suivant l'admission en U.S.I.) ([aide pour les définitions](#))

SAPS II =

(la valeur peut être entrée directement)

DISTRIBUTIONS DES PATIENTS PAR CLASSES D'IGS II



<p>Température</p> <input type="text"/> <input type="text" value="0"/>	<p>Pression Art. Moyenne</p> <input type="text"/> <input type="text" value="0"/>	<p>Fréq. Cardiaque</p> <input type="text"/> <input type="text" value="0"/>
<p>Fréq. Respiratoire</p> <input type="text"/> <input type="text" value="0"/>	<p>Si FIO2 >= 0,5 : Grad. (A-a)O2 Aide au calcul</p> <input type="text"/> <input type="text" value="0"/>	<p>Si FIO2 < 0,5 : PaO2</p> <input type="text"/> <input type="text" value="0"/>
<p>Si pH indisponible: HCO3⁻</p> <input type="text"/> <input type="text" value="0"/>	<p>pH Artériel</p> <input type="text"/> <input type="text" value="0"/>	<p>Natrémie</p> <input type="text"/> <input type="text" value="0"/>
<p>Kaliémie</p> <input type="text"/> <input type="text" value="0"/>	<p>Créatinémie avec IRA</p> <input type="text"/> <input type="text" value="0"/>	<p>Créatinémie sans IRA</p> <input type="text"/> <input type="text" value="0"/>
<p>Hématocrite</p> <input type="text"/> <input type="text" value="0"/>	<p>Leucocytes</p> <input type="text"/> <input type="text" value="0"/>	<p>Glasgow Aide au calcul</p> <input type="text"/> <input type="text" value="0"/>
<p>Age</p> <input type="text"/> <input type="text" value="0"/>	<p>Total Apache II</p> <input type="text" value="0"/> <input type="button" value="Effacer"/>	<p>Défaillance viscérale chronique (Aide) immunodépression</p> <input type="text"/> <input type="text" value="0"/>

Calcul du score SOFA

(Sequential Organ Failure Assessment)

Respiration <input type="text"/> 0	Coagulation <input type="text"/> 0
Cardiovasculaire <input type="text"/> 0	Glasgow (aide) <input type="text"/> 0
Hépatique (bilirubine) <input type="text"/> 0	Rein (créat ou diurèse) <input type="text"/> 0
Total SOFA= <input type="text"/> <input type="button" value="Effacer"/>	

Les paramètres sont évalués quotidiennement.

Respiration

PaO₂/FiO₂ (mmHg)

< 400 +/- ventilation assistée

< 300 +/- ventilation assistée

< 200 et ventilation assistée

< 100 et ventilation assistée

Cardiovasculaire

(Catéchol. en gamma/kg.min)

PAM < 70 mmHg

Dopa < ou = 5 ou Dobutamine

Dopa > 5 ou Ad / Norad < ou = 0,1

Dopa > 15 ou Ad / Norad > 0,1

Glasgow (aide)

0

at ou diurèse)

13-14

10-12

6-9

< 6

Coagulation

(Plaq X 10³/mm³)

< 150

< 100

< 50

< 20

Hépatique (bilirubine)

(mg/L.....micromol/L)

12-19.....20-32

20-59.....33-101

60-119.....102-204

> 12..... > 204

Rein (créat ou diurèse)

0

Effacer

(mg/L.....micromol/L)

12-19.....110-170

20-34.....171-299

35-49...300-440 ou < 500 mL/j

> 50..... > 440 ou < 200 mL/j

<p>FC <input type="text" value="0"/></p> <p>Pression Artérielle Systolique <input type="text" value="0"/></p>	<p>Leucocytes <input type="text" value="0"/></p> <p>Plaquettes <input type="text" value="0"/></p>	<p>Urée Sanguine <input type="text" value="0"/></p> <p>ou Azote uréique sérique <input type="text" value="0.28 - 0.55 g/L"/></p> <p>Créatinine <input type="text" value="0"/></p> <p>Diurèse <input type="text" value="0"/></p>
<p>Système Respiratoire</p>	<p>Neurologie</p>	
<p>PaO2/FiO2 <input type="text" value="0"/></p>	<p>Score de Glasgow (Aide) <input type="text" value="0"/></p>	
<p>Système Hépatique</p>		<p>Score LODS (Aide) <input type="text" value="0"/></p>
<p>Bilirubine <input type="text" value="0"/></p> <p>Prothrombine <input type="text" value="0"/></p>	<p>Score Cardiovasculaire <input type="text" value="0"/></p> <p>Score Hématologique <input type="text" value="0"/></p> <p>Score hépatique <input type="text" value="0"/></p> <p>Score Neurologique <input type="text" value="0"/></p> <p>Score Rénal <input type="text" value="0"/></p> <p>Score Respiratoire <input type="text" value="0"/></p>	<p>Mortalité Prédite <input type="text" value="0"/></p> <p>Effacer</p>

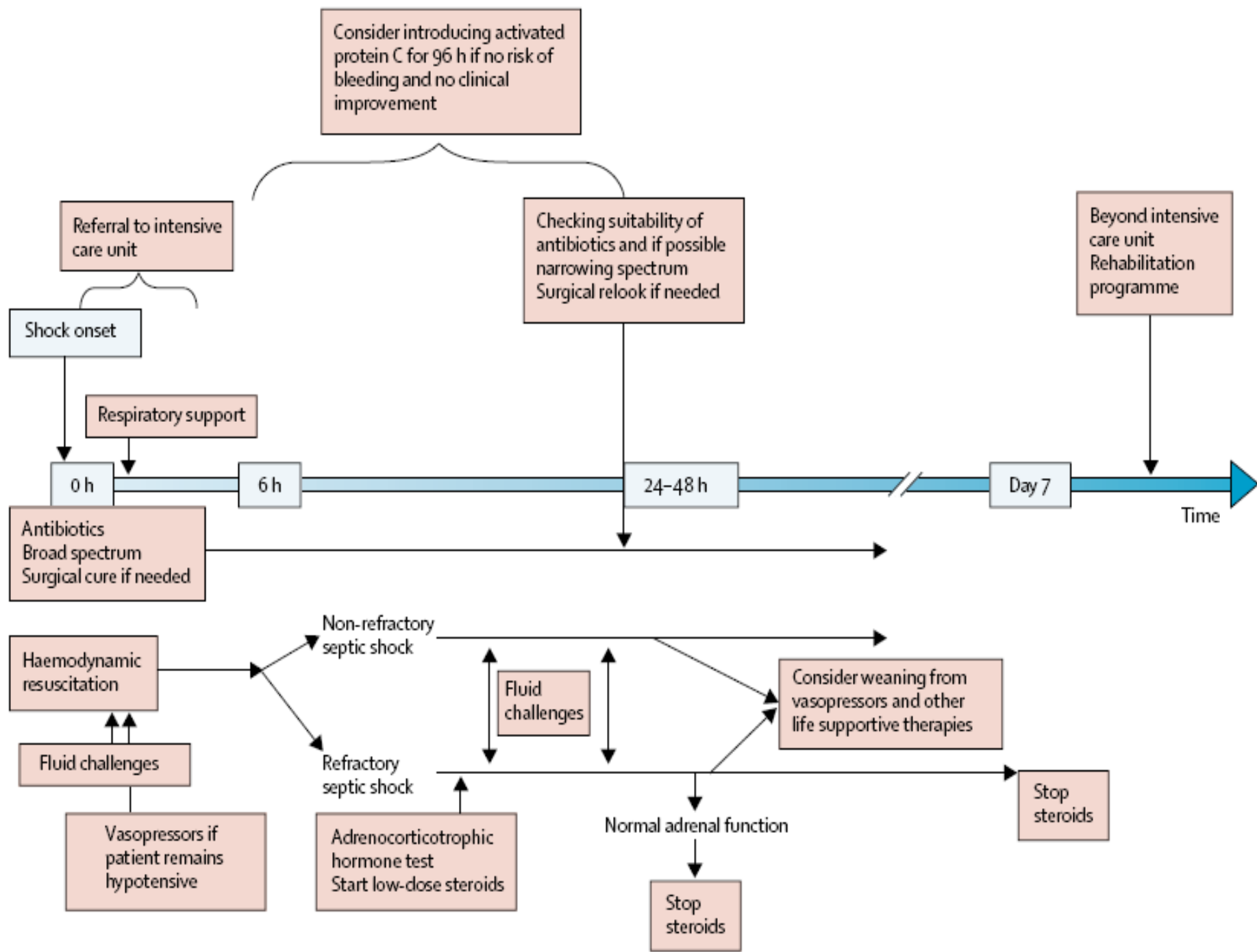
La formule utilisée est : $Logit = -3.4043 + 0.4173*(LODS)$. Probabilité de mortalité = $(e^{Logit}) / (1 + e^{Logit})$

Characteristics at inclusion (1)

	PCT (=307)	Controls (n=314)
Age, y	61.0±15.2	62.1±15.0
Males, n (%)	207 (67)	204 (65)
McCabe2/3, n (%)	142 (46)	136 (43)
Medical, n (%)	275 (89)	280 (89)
Origin		
ER	144 (47)	168 (53)
Med/Surg	138 (45)	119 (38)
ICU	25 (8)	27 (9)
Immunosuppression	44 (14)	49 (16)

Characteristics at inclusion (2)

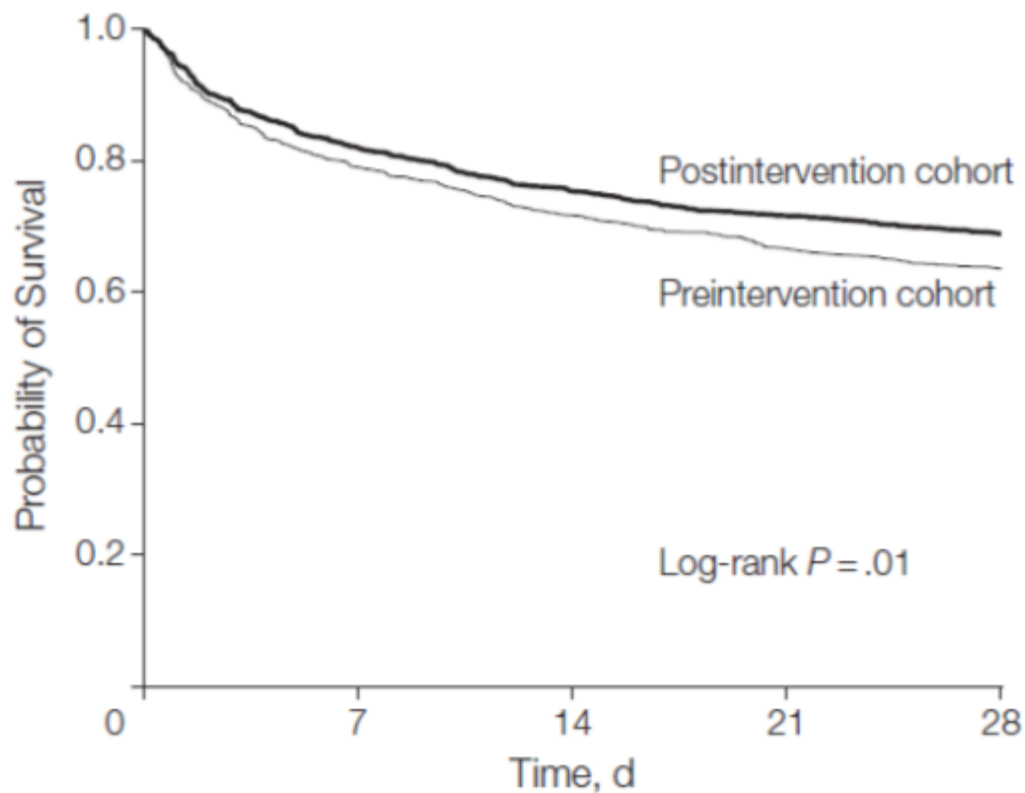
	PCT (=307)	Controls (n=314)
SAPS II score	43.8±16.1	43.4±15.4
SOFA score	7.5±4.4	7.2±4.4
Mechanical ventilation, n (%)	211 (69)	208 (66)
Septic shock, n (%)	131(43)	123 (39)
Community-acquired infection, n (%)	153 (50)	173 (55)
Nosocomial infection, n (%)	154 (50)	141 (45)
Positive BC, n (%)	55 (18)	53 (17)



A. Source Control

Source Control Technique	Examples
Drainage	<ul style="list-style-type: none">● Intra-abdominal abscess● Thoracic empyema
Debridement	<ul style="list-style-type: none">● Septic arthritis● Pyelonephritis, cholangitis● Infected pancreatic necrosis● Intestinal infarction● Mediastinitis
Device removal	<ul style="list-style-type: none">● Infected vascular catheter● Urinary catheter● Infected intrauterine contraceptive device
Definitive control	<ul style="list-style-type: none">● Sigmoid resection for diverticulitis● Cholecystectomy for gangrenous cholecystitis● Amputation for clostridial myonecrosis

Figure. Probability of Survival in Patients With Severe Sepsis in the Preintervention and Postintervention Cohorts According to the Length of Survival



No. at risk						
Preintervention	854	675	613	569	543	
Postintervention	1465	1201	1105	1050	1009	

The Sepsis Six— to be delivered within 1 h

- (1) Deliver high-flow oxygen
- (2) Take blood cultures and other cultures, consider source control
- (3) Administer empirical intravenous (IV) antibiotics
- (4) Measure serum lactate or alternative
- (5) Start IV fluid resuscitation using Hartmann's or equivalent
- (6) Commence accurate urine output measurement