Lower respiratory tract infection with *Staphylococcus aureus* in sickle-cell adult patients with severe acute chest syndrome - the STAPHACS Study

Alexandre Elabbadi,[1] Guillaume Voiriot,[1,2] Anne Tristan,[3,4] Aude Gibelin,[1] Charlotte Verdet,[5] Michel Djibré,[1] Aline Santin,[6] Etienne-Marie Jutant,[1] Julien Lopinto,[1] François Vandenesch,[3,4] François Lionnet[6] and Muriel Fartoukh[1,2]

[1]*Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Service de Médecine Intensive Réanimation, Hôpital Tenon, Paris;* [2]*Groupe de Recherche Clinique CARMAS, Collegium Galilée, Créteil;* [3]*Centre National de Référence des Staphylocoques, Institut des Agents Infectieux, Hospices Civils de Lyon, Lyon;* [4]*Centre International de Recherche en Infectiologie, INSERM U1111, Université Lyon 1, École Normale Supérieure de Lyon, Lyon;* [5]*Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Service de Bactériologie, Hôpital Saint-Antoine, Paris and* [6]*Sorbonne Université, Assistance Publique - Hôpitaux de Paris, Service de Médecine Interne, Centre de Référence de la Drépanocytose, Hôpital Tenon, Paris, France*

Correspondence: ALEXANDRE ELABBADI - alexandre.elabbadi@aphp.fr

ELECTRONIC SUPPLEMENTARY MATERIAL

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- the STAPHACS Study -

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Content

Variables	*S. aureus* ACS group, n=29	Control ACS group, n=48	p value
Age (years), median [IQR]	24 [21–28]	24 [22–31]	0.58
Male, n (%)	16 (55)	31 (65)	0.41
Type of hemoglobinopathy, n (%)¶			
Homozygous SS	25 (86)	43 (90)	0.72*
Heterozygous SC	2 (7)	1 (2)	0.55*
Sβ-thalassemia	2 (7)	4 (8)	0.99*
Laboratory data at baseline, median [IQR]			
Hemoglobin (g/dL)	8 [7.8–9]	8.5 [8–9.5]	0.20
Fetal hemoglobin (%)	7.4 [2.3–15.1]	9.5 [5.8–13.5]	0.54
Lactate dehydrogenase (IU/L)	413 [340–506]	432 [390–515]	0.33
Creatinine (μmol/L)	45 [37–58.5]	51 [41–60]	0.22
Sickle cell disease complications, n (%)			
History of ACS	24 (83)	38 (79)	0.70
History of alloimmunization	7 (28)	5 (14)	0.20*
Retinopathy	7 (26)	21 (44)	0.13
Cerebral vasculopathy	2 (7)	4 (8)	0.99*
Pulmonary hypertension	3 (10)	2 (4)	0.36*
Priapism	4 (25)	4 (13)	0.42*
Leg ulcer	2 (7)	1 (2)	0.55*
Chronic kidney disease	2 (7)	2 (4)	0.63*
Gallstone	17 (59)	32 (67)	0.48*
Splenectomy	5 (17)	5 (10)	0.49*
Long-term treatment, n (%)			
Folic acid supplements	28 (100)	47 (98)	0.99*
Hydroxycarbamide	20 (69)	31 (65)	0.69
Transfusion program	2 (7)	0	0.14*
Long-term antibiotics	1 (3)	2 (4)	0.99*
Iron chelator	3 (10)	1 (4)	0.15*
Vaccination, n (%) †			
Influenza vaccination	5 (17)	8 (17)	0.99*
Pneumococcal vaccination	22 (76)	34 (71)	0.63
Pneumococcal polysaccharide vaccination (PPSV23) alone	15 (52)	17 (35)	0.16
Prevenar 13 vaccination alone	0	8 (17)	**0.02***
Combined vaccination strategy	7 (24)	9 (19)	0.57
History of *Staphylococcus aureus* infection, n (%)	8 (28)	3 (6)	**0.01***
Pulmonary	5 (17)	2 (4)	
Catheter and Port-a-Cath	1 (3)	0 (0)	
Skin and soft tissue	1 (3)	0 (0)	
Bone	1 (3)	1 (2)	
Symptoms before hospitalization			
Influenza epidemic period§, n (%)	7 (24)	17 (35)	0.30
Time from onset of symptoms to ICU admission (days), median [IQR]	3 [2–6]	3 [2–6]	0.70
Time from ward admission to ICU referral (days), median [IQR]	2 [1–4]	1 [0–3]	0.44
Clinical characteristics of ACS			
Respiratory rate (/minute), median [IQR]	29 [25–36.8]	27 [24–30]	0.24
Temperature (°C), median [IQR]	38.1 [37.5–38.5]	37.7 [37–38.4]	0.20
Visual analog pain scale (points), median [IQR]	7 [5.8–8]	7 [5–8]	0.59
Chest pain, n (%)	25 (89)	40 (83)	0.74*
Limb pain, n (%)	18 (64)	29 (60)	0.74
Bronchial breath sounds, n (%)	8 (28)	16 (33)	0.60
Rales, n (%)	20 (69)	31 (65)	0.69
Wheezing, n (%)	2 (7)	4 (8)	0.99*
Hemoptysis, n (%)	1 (3)	1 (2)	0.99*
Golden sputum, n (%)	16 (55)	22 (46)	0.43
Laboratory data on ICU admission, median [IQR]			
Hemoglobin (g/dL)	7.2 [6.4–7.9]	7.4 [6.5–8.4]	0.89
WBC (10^9/L)	18 [12.6–20.7]	18.9 [14.6–21.9]	0.56
Platelets (10^9/L)	277 [165–386]	264 [221–340]	0.91
Partial pressure of oxygen (mmHg)	94 [74–102]	92 [65–119]	0.83
Corresponding FiO_2 administration (%)	32 [28–42]	38 [28–44]	0.41
Lactate dehydrogenase (IU/L)	607 [423–1011]	665 [401–1138]	0.94
Aspartate aminotransferase (IU/L)	76 [41–105]	56 [38–98]	0.35
Alanine aminotransferase (IU/L)	42 [27–62]	32 [18–52]	0.08
Prothrombin ratio (%)	66 [58–73]	70 [65–77]	0.11
Creatinine (μmol/L)	46 [34–57]	51 [42–63]	0.14
C-reactive protein (mg/L)	131 [82–178]	169 [74–235]	0.67
Severity score, median [IQR]			
SAPS II	17 [13–19]	16 [10–21]	0.31
SOFA	3 [3–4]	3 [3–4]	0.47

Chest x-ray on ICU admission			
Number of lobes involved, median [IQR]	2 [2–3]	2 [1.8–2.3]	0.68
Bilateral involvement, n (%)	21 (72)	33 (69)	0.73
Excavated lesion, n (%)	0	0	
Pleural effusion, n (%)	6 (21)	11 (23)	0.82
Treatment during ICU stay, n (%)			
Oxygen	28 (100)	48 (100)	0.99*
Morphine	27 (96)	48 (100)	0.37*
Ketamine	13 (45)	25 (52)	0.54
Antibiotics	29 (100)	48 (100)	0.99*
Oseltamivir	6 (21)	7 (15)	0.54*
Transfusion	14 (48)	27 (56)	0.50
Therapeutic anticoagulation	5 (17)	10 (21)	0.70
Bronchodilator	1 (3)	5 (10)	0.40*
Complications during ICU stay, n (%)			
Ventilatory support[#]	3 (10)	10 (21)	0.35*
High flow nasal oxygen therapy	2 (7)	9 (19)	0.19*
Noninvasive positive pressure ventilation	0 (0)	2 (4)	0.52*
Invasive ventilation	2 (7)	4 (8)	0.99*
Vasopressors	1 (3)	3 (6)	0.99*
Acute renal failure[$]	6 (21)	8 (17)	0.72
Death	0 (0)	1 (2)	0.99*
Length of stay (days), median [IQR]			
ICU	4 [3–6]	4 [3–5.2]	0.80
Hospital	10 [9–16]	10.5 [8–13.3]	0.58

Supplementary Table 1: Baseline characteristics and ACS characteristics

[¶] Heterozygous alpha thalassemia was associated in 9 episodes

[†] Missing case data: influenza vaccination = 8/29; pneumococcal vaccination = 5/29. Missing 'control' data: influenza vaccination = 9/48; pneumococcal vaccination = 6/48.
The time between the pneumococcal vaccination and the occurrence of severe episode of ACS was 2 years [0-4].

[§] The flu season period extended from January 12, 2015 to March 15, 2015; January 18, 2016 to April 10, 2016; October 3, 2016 to April 9, 2017.[32]

[#] Including high flow nasal oxygen therapy, non-invasive and invasive mechanical ventilation. Some patients may have received several ventilatory supports.

[$] Acute renal failure defined as an increase in serum creatinine of more than 26.4 μmol/L or an increase of more than 1.5 times the baseline serum creatinine with the use of renal replacement therapy. One patient required renal replacement therapy (in the control group).

Data are presented as median [first through third quartiles] or number (%). Continuous variables are compared using a Wilcoxon method; categorical variables are compared either using a χ^2 test or Fisher's exact test (
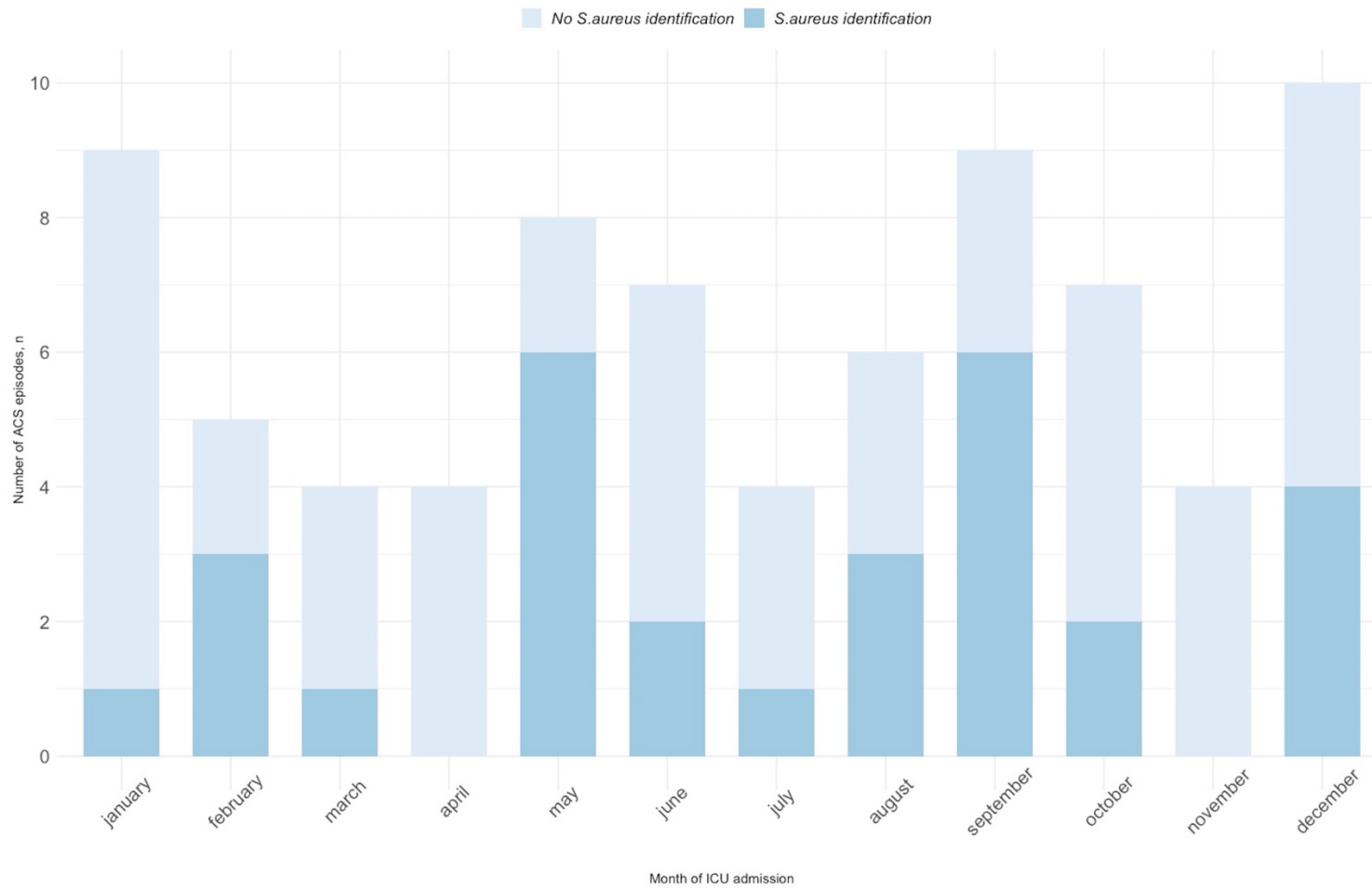
Supplementary Figure 1: Distribution of all acute chest syndrome episodes, contrasting the identification of Staphylococcus aureus

During the 3-year study period, the flu season extended from January 12, 2015 to March 15, 2015; January 18, 2016 to April 10, 2016; October 3, 2016 to April 9, 2017 in France (https://www.santepubliquefrance.fr).
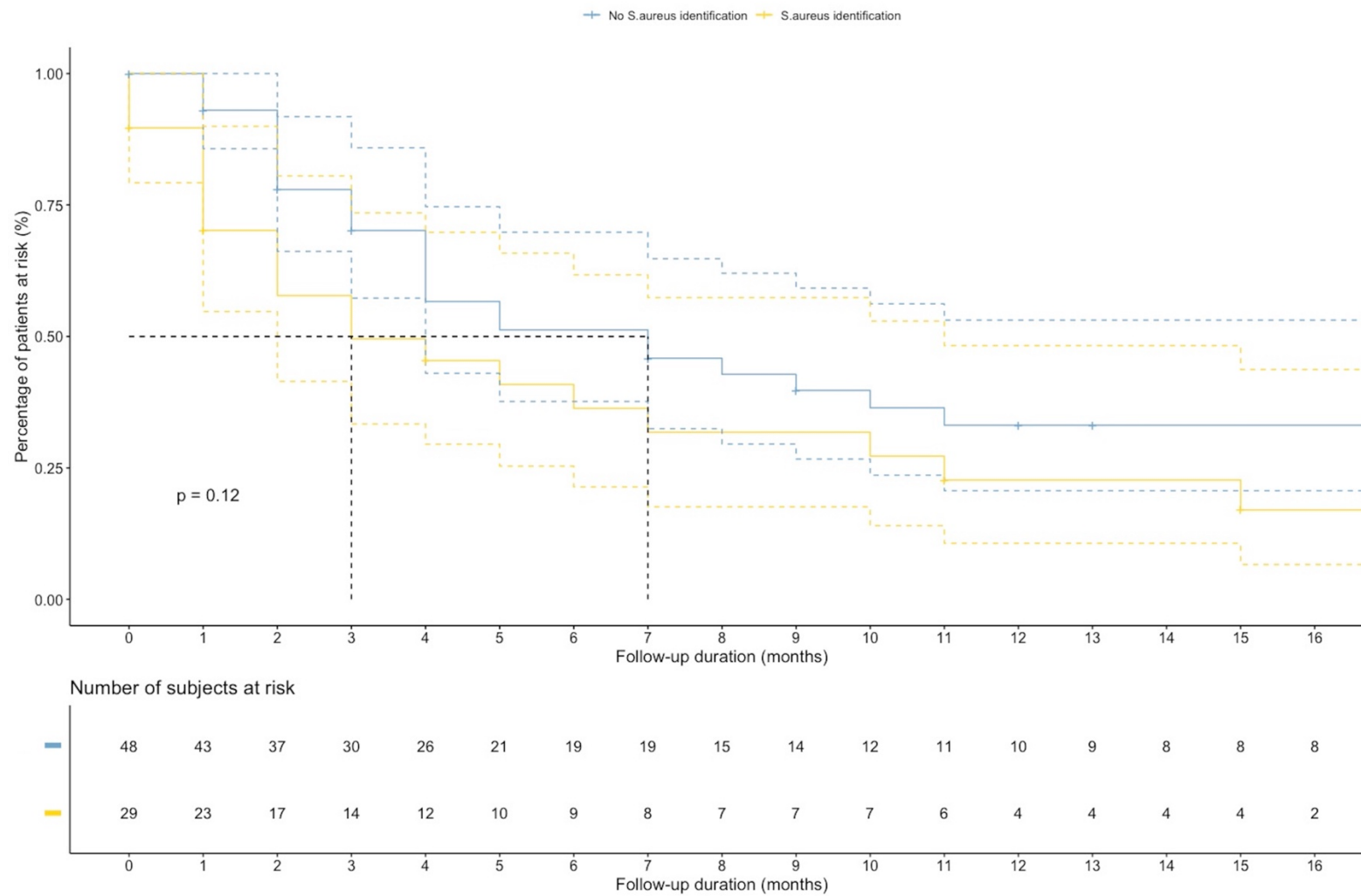
Supplementary Figure 2: Kaplan-Meier curve for readmission for acute chest syndrome or vaso-occlusive crisis following the index hospitalization