Michal Holub

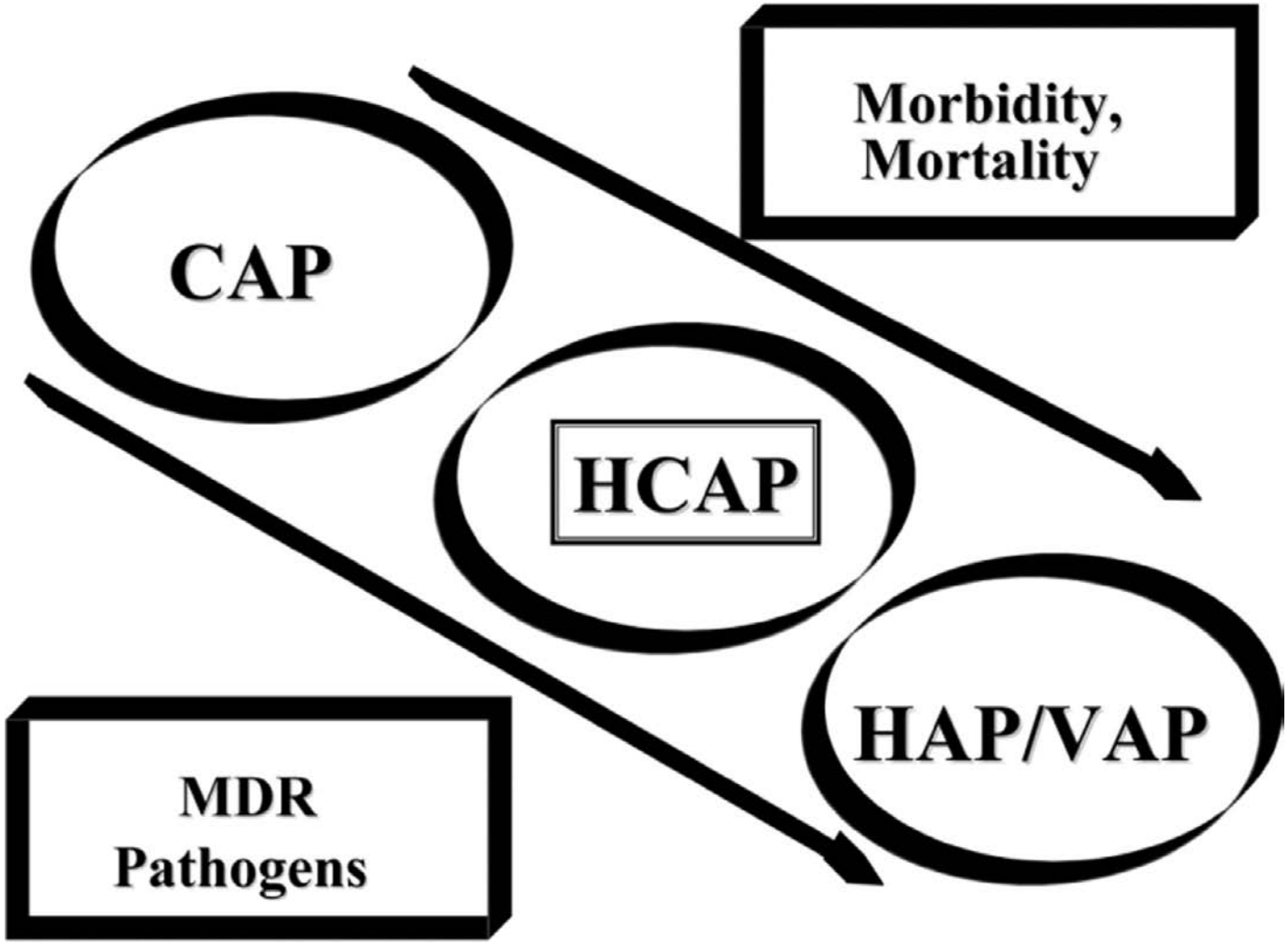
Department of Infectious Diseases

NOSOCOMIAL RESPIRATORY INFECTIONS IN ICU

AND

DYSREGULATED LUNG IMMUNITY

RELATIONSHIPS OF HEALTH CARE ASSOCIATED PNEUMONIA (HAP)



Kollef MH et al. Clin Infect Dis. 2008;46:S296-334.

HAP AND „ESKAPE“ PATHOGENES

E*nterobacter faecium*

S*taphylococcus aureus,* incl. MRSA

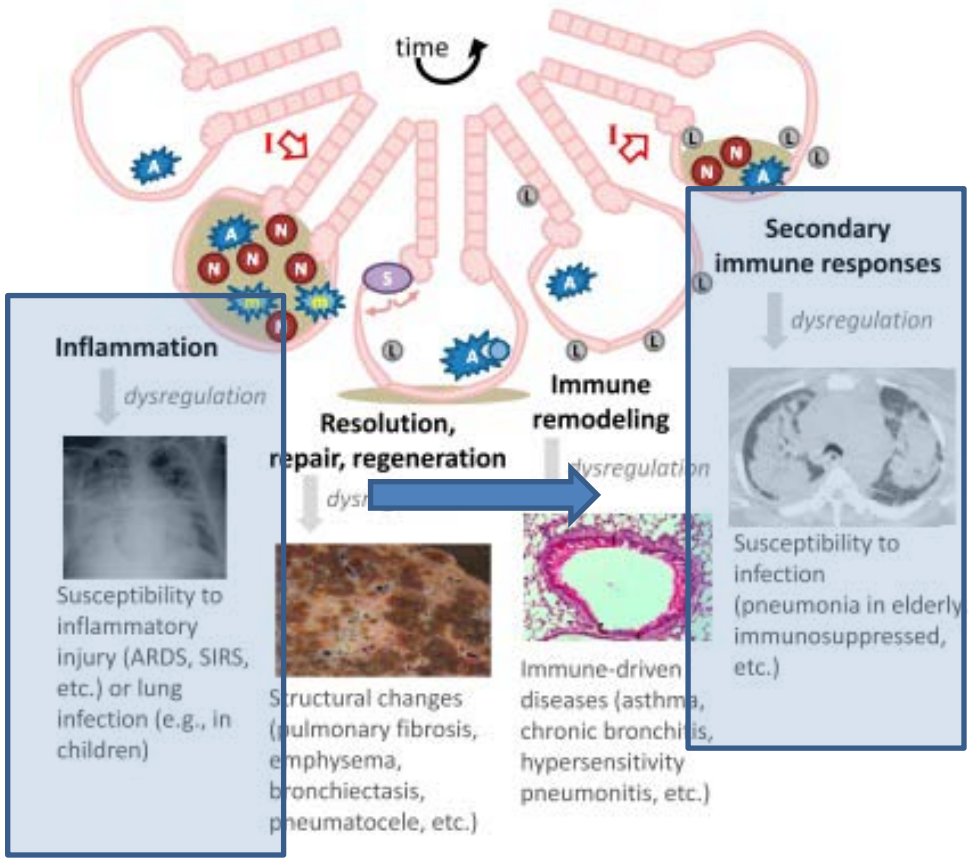
K*lebsiella pneumoniae*

A*cinetobacter baumannii*

P*seudomonas aeruginosa*

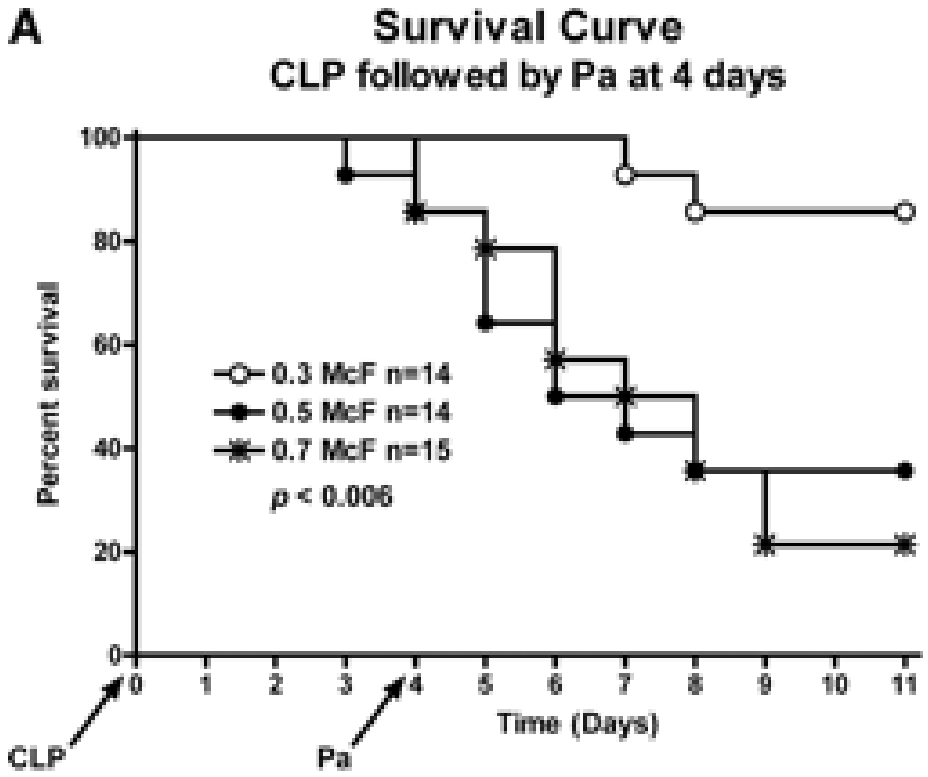
E*scherichia coli*

LUNG IMMUNE REMODELLING AFTER INFLAMMATION AND INFECTION



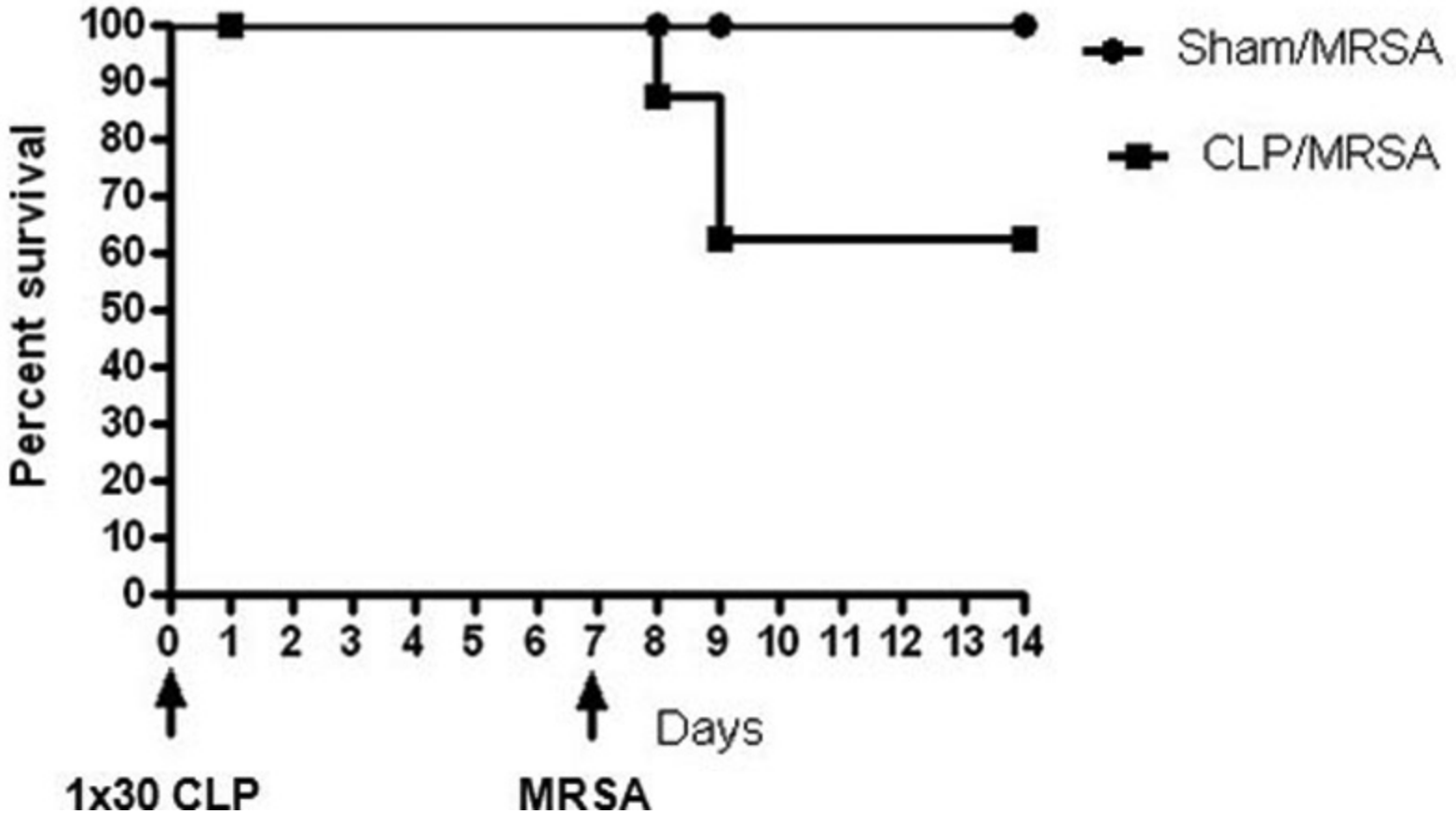
Mizgerd JP. Am Respir Crit Care Med. 2012; 186: 824-9.

Murine respiratory infection due to *P. aeruginosa* after CLP



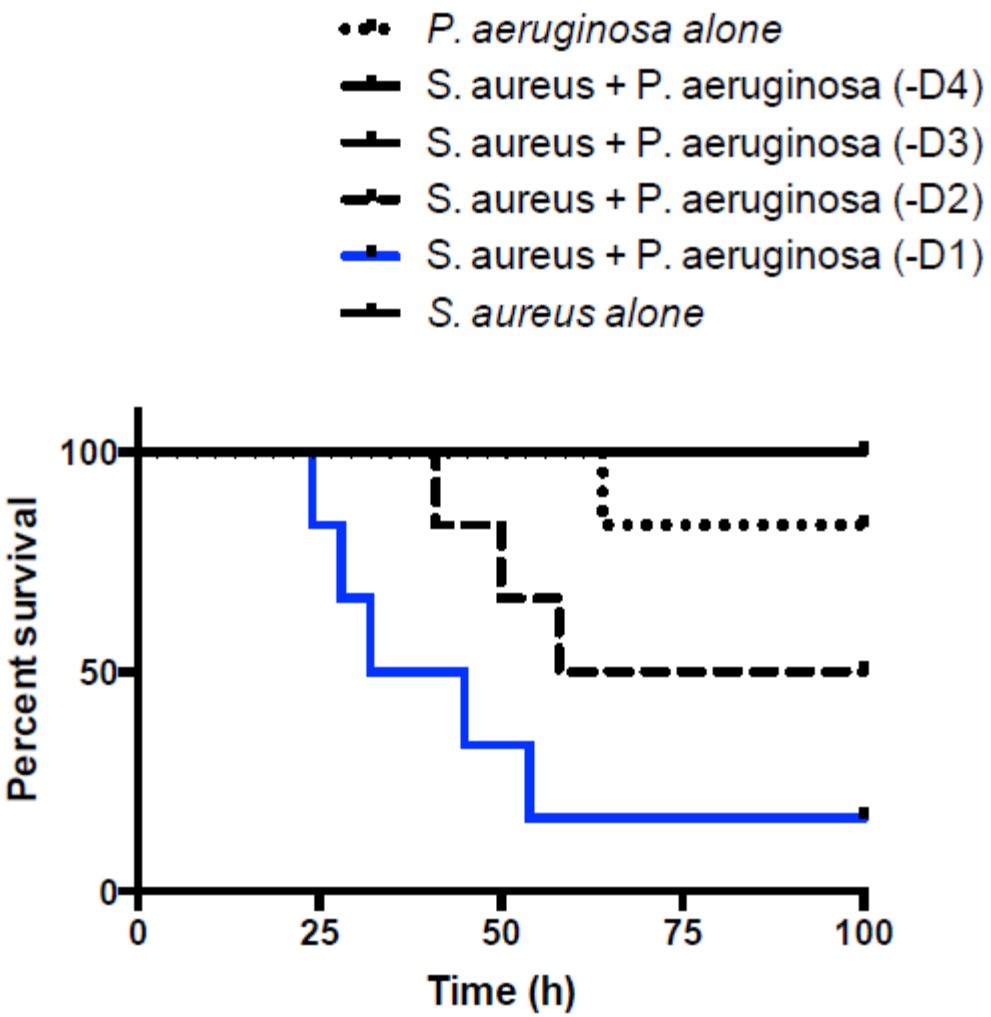
Muenzer JT et al. Infect Immun. 2010;78:1582-92.

Murine respiratory infection due to MRSA after CLP



Jung E et al. Shock 2012;37:85-94.

Double hit model of *S. aureus* infection and *P. aeruginosa* superinfection



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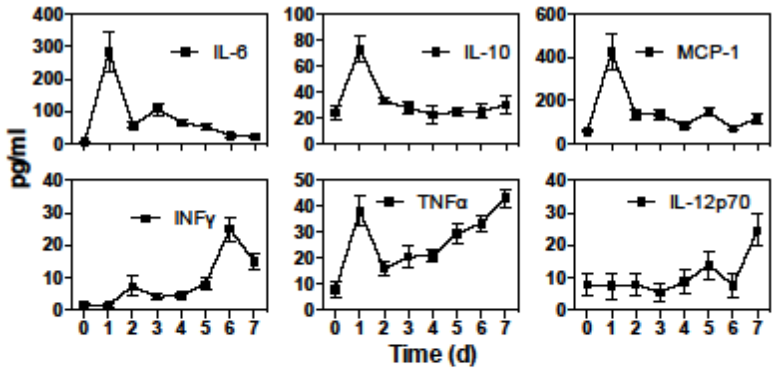
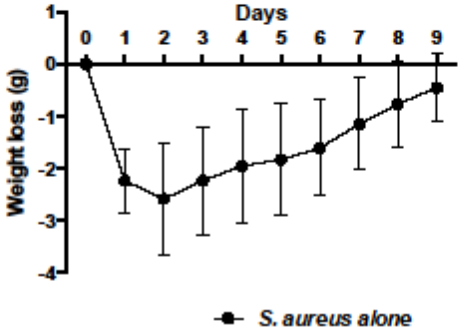




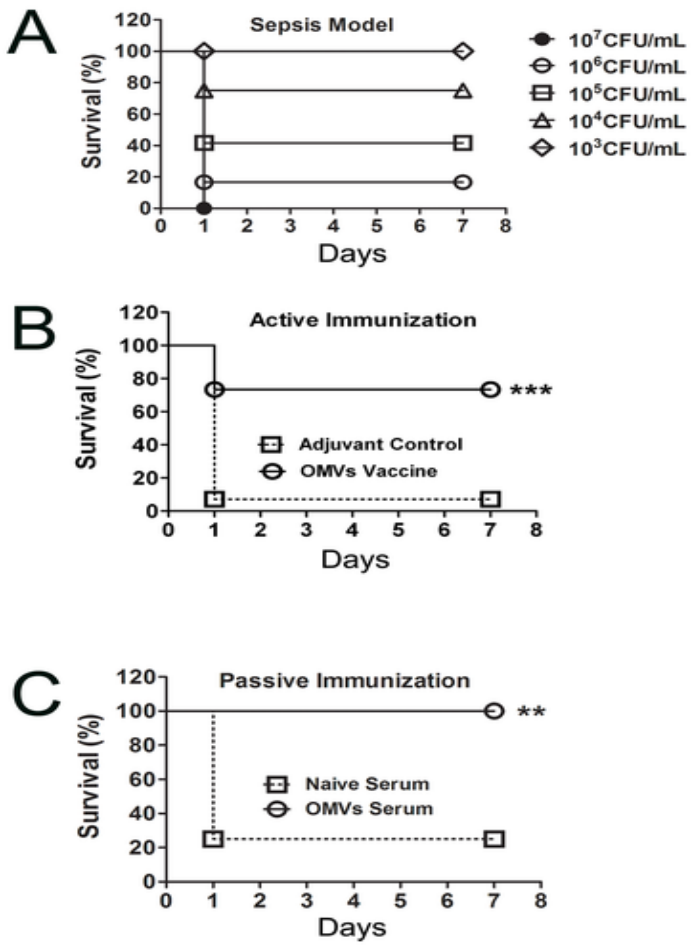
Murine respiratory infection due to *S. aureus* after LPS challenge

Lung-derived lymphocytes				
Cells[b]	SHAM $n = 5$	LPS+SHAM $n = 3$	*S. aureus* $n = 9$	LPS+*S. aureus* $n = 8$
T	238 ± 45‡	148 ± 72	377 ± 35	165 ± 30‡
$CD4^+$ T	175 ± 40	82 ± 2	305 ± 44	139 ± 27‡
$CD8^+$ T	72 ± 2	66 ± 12	121 ± 22	61 ± 13
B	184 ± 25	186 ± 14	233 ± 28	126 ± 26
NK	103 ± 13	131 ± 29	124 ± 18	127 ± 38

	S. aureus	LPS+*S. aureus*
CFU/mL	1910 ± 100	78 ± 12

Holub M et al. Folia microbiol. 2006;51:469-72.

Experimental murine respiratory infection due to *A. baumannii*



Huang W at al. PLoS ONE 2015; 9: e100727.

HAP AND POTENTIAL IMMUNE PREDICTORS

Decresed naive CD4+ and CD8+ T cell counts

Higher memory and terminally differentiated CD8+ T cells

Combined dysfunction of monocytes, neutrophils and T cells

Deactivation of alveolar macrophages

HAP AND IMMUNE RISK PHENOTYPE (IRP)

IRP criteria***(n = 240)				
CD4/CD8 < 1 (n = 245)	20 (8.2)	10 (10.5)	10 (6.7)	0.34
CD8 T-cells > 600 (n = 245)	32 (13.1)	17 (17.9)	15 (10.0)	0.07
CD28-CD8+ T-cells > 300 (n = 238)	64 (26.9)	31 (33.3)	33 (22.8)	0.07
Positive CMV serology (n = 246)	193 (78.5)	76 (79)	117 (78)	0.87
Positive IRP (n = 240, 95/145)	60 (25)	29 (30.5)	31 (21.4)	0.11

Nosocomial pneumonia in the IRP+ group 28.3% vs. 15.6% in IRP- group; $p = 0.036$.

Plonquet A et al. Immun Ageing. 2011;8:8.

COMBINED DYSFUNCTION OF IMMUNE CELLS - COHORT DESCRIPTION

Table 1 Site of infections acquired in ICU

Confirmed infections	Pneumonia-10 (7 VAP) BSIs-4 Catheter-related BSIs-3 UTIs-5 Surgical site/soft tissue infections-4
Probable infections	Pneumonia-4 (all VAP) Intra-abdominal infection-3

Table 2 Culture results from patients with confirmed, suspected and unlikely infections. More than one organism was isolated from some patients

Infection category	Organism	Frequency
Confirmed	*Staphylococcus aureus*	3
	Coagulase negative *Staphylococci*	1
	Streptococcus pneumoniae	1
	Other *Streptococci*	1
	Enterococcus faecalis	2
	Burkholderia cepacia	1
	Citrobacter braakii	1
	Coliform—no further specification	1
	Enterobacter cloacae	3
	Escherichia coli	5
	Klebsiella pneumoniae	2
	Haemophilus influenzae	1
	Pseudomonas aeruginosa	3
	Anaerobes	1
	Candida albicans	4
	Herpes simplex	1
Probable	*Staphylococcus aureus*	1
	Culture negative	4
	No samples obtained as care withdrawn	2
Unlikely	*Staphylococcus aureus*	2
	Coagulase negative *Staphylococci*	2
	Streptococcus pneumoniae	1
	Acinetobacter baumannii	1
	Haemophilus influenzae	1
	Klebsiella pneumoniae	1
	Candida albicans	1
	Culture negative	2

Morris AC. Br J Anaesth. 2013;111:778-87.

HAP AND COMBINED IMMUNE DYSFUNCTION

Table 4 Cox model for occurrence of nosocomial infection. *Elevated Treg cells were expressed as a time-dependent co-variate. NA, not applicable

Variable	*P*-value	HR (95% CI)
Overall model	0.001	NA
*Elevated Tregs	0.026	2.4 (1.1–5.4)
Neutrophil dysfunction	0.009	6.9 (1.6–30)
Blood transfusion	0.002	0.3 (0.1–0.6)

Table 5 The relationship between the burden of immune dysfunction and acquisition of nosocomial infection [*i.e. neutrophil dysfunction (as indicated by low CD88), monocyte deactivation (as indicated by low HLA-DR) and elevated regulatory T-cells]. $P=0.0004$ by χ^2 test for trend

Number of dysfunctions*	*n*	% Acquiring nosocomial infection (95% CI)
0	11	0 (0–0)
1	21	10 (0–22)
2	43	37 (23–52)
3	20	75 (56–94)

Morris AC. Br J Anaesth. 2013;111:778-87.

DYSFUNCTION OF ALVEOLAR MACROPHAGES AS PREDICTOR OF HAP

Table 3 HLA-DR expression (antibody/cell) on peripheral blood monocytes and AMs

	Peripheral blood monocytes			AMs		
Time point	Preoperative	Postoperative	p	Preoperative	Postoperative	*P*
All (n = 31)	26,587 (20,410, 31,478)	13,996 (11,724, 17,706)	0.001[a]	985,234 (698,683, 1,293,531)	712,564 (320,726, 941,120)	0.001[a]
Group 1 (n = 28)	26,266 (20,646, 31,415)	15,258 (12,365, 18,580)	0.001[a]	1,009,337 (739,280, 1,294,545)	736,306 (430,604, 943,491)	0.002[a]
Group 2 (n = 3)	27,882 (12,325, 34,088)	10,292 (10,288, 13,389)	n	652,262 (505,628, 985,234)	106,139 (42,434, 417,111)	n/a

HLA-DR expression on peripheral blood monocytes as well as on AMs was significantly reduced after surgery. In group 2 a strong reduction without statistical significance was seen. Data are given as medians and IQR in brackets. The Wilcoxon test was used to calculate significant difference for the depending variables; [a]statistically significant difference. HLA-DR, human leukocyte antigen-DR; AM, alveolar macrophage.

Chalk K et al. Crit Care. 2013; 17: R285.