Septic shock-3 versus septic shock-2: looking back at the ALBIOS trial

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Argomento: Altro

Background The *post-hoc* analysis of patients enrolled into the ALBIOS trial – which tested the use of albumin and crystalloids versus crystalloids alone in severe sepsis and septic shock – suggested that patients with shock (Shock-2) had a survival benefit when treated with albumin. The new septic shock definition (Shock-3) added the criterion of a lactate threshold of 2 mmol/L. We investigated how the Shock-2 and Shock-3 populations differed and whether the albumin benefit would be confirmed. **Methods** We analysed data from 1741 ALBIOS patients with serum lactate measurement available at baseline. We compared group size, physiological variables and 90-day mortality between Shock-2 and Shock-3 and between albumin and crystalloids treatment groups.**Results** The Shock-3 definition decreased the shock population size by 34%. The Shock-3 group had higher lactate ($p<0.001$), greater resuscitation fluid requirement (0.014), higher SAPS II ($p<0.001$) and SOFA scores ($p=0.022$), lower platelet count ($p=0.002$) and higher 90-day mortality (46.7% vs 51.9%; $p=0.031$) (Table 1). The albumin administration in Shock-2 patients led to significantly lower mortality compared to crystalloids (43.5% vs 49.9%; $p=0.04$). Despite similar effect size (6%), this benefit was no longer statistically significant in Shock-3 (48.7% vs 54.9%; $p=0.22$; *post-hoc* power 38.4%)(Figure 1). To prove significant a 6% mortality difference at a power of 80% – assuming a 50% expected mortality – 2170 shock patients are required. With a recruitment rate of 0.5 patient/unit/month – as estimated from previous trials (Table 2) – a study with 30 participating centres would last 12 years.**Conclusions** In this *post-hoc* ALBIOS analysis, the Shock-3 definition selected a more severe population, it greatly reduced the number of shock patients so that the benefits of albumin – although similar in magnitude – were no longer significant. Furthermore, the *a priori* exclusion of patients with lactate <2mmol/L would lead to trial feasibility issues.

Table 1. Shock-2 vs Shock-3.

Variables	N	Shock 2	N	Shock 3	P
	1098		721		
MAP (mmHg)	1098	71 ± 14	721	70 ± 14	0.055
CVP (mmHg)	1030	10.5 ± 4.8	686	10.5 ± 4.8	1
HR (bpm)	1098	106 ± 21	721	110 ± 21	0.005
SvO2 (%)	982	72 ± 11	661	72 ± 11	0.462
PaCO2 (mmHg)	1087	39.2 ± 11.1	716	38.4 ± 10.6	0.128
PvCO2 (mmHg)	978	46.5 ± 11.5	657	45.8 ± 11.3	0.225
Noradrenaline (µg/kg/min)	1098	0.33 ± 0.36	617	0.36 ± 0.39	0.093
Patients on vasoactive drugs (%)	1098	100	721	100	1
Lactate (mmol/L)	1098	3.9 ± 3.29	721	5.22 ± 3.36	<0.001
pH	1086	7.36 ± 0.1	716	7.35 ± 0.11	0.046
BE (mmol/L)	1086	-3.8 ± 6.1	716	-4.68 ± 6.16	0.003
Albumin (g/L)	996	23.6 ± 6.2	655	23.3 ± 6.3	0.339
Creatinine (mg/dL)	1094	2.17 ± 1.63	719	2.23 ± 1.54	0.433
Diuresis (ml/h)	1098	71.64 ± 73.85	721	69 ± 75.7	0.467
Fluid balance (6h) (L)	1077	1.23 ± 1.52	721	1.43 ± 1.66	0.027
Fluid input (day 1) (L)	1004	4.8 ± 2.3	640	5.1 ± 2.4	0.014
SOFA	1058	8.95 ± 4.8	696	9.4 ± 2.4	0.022
SAPS II	1098	52.4 ± 17	721	55.7 ± 17.1	<0.001
Mortality (90d)(%)	46.7		51.9		0.031
WBC	1097	13.3 ± 10.6	720	12.7 ± 11.3	0.283
PLT	1098	179 ± 124	721	160 ± 119	0.002

Physiological and outcome variables (means ± standard deviation) measured at baseline in patients classified according to Shock-2 or Shock-3 criteria. MAP, mean arterial pressure; CVP, central venous pressure; HR, heart rate; SvO2, central venous saturation; PaCO2, arterial CO2 partial pressure; PvCO2, venous CO2 partial pressure; BE, base excess; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; WBC, white cell count; PLT, platelet count.

Figure 1

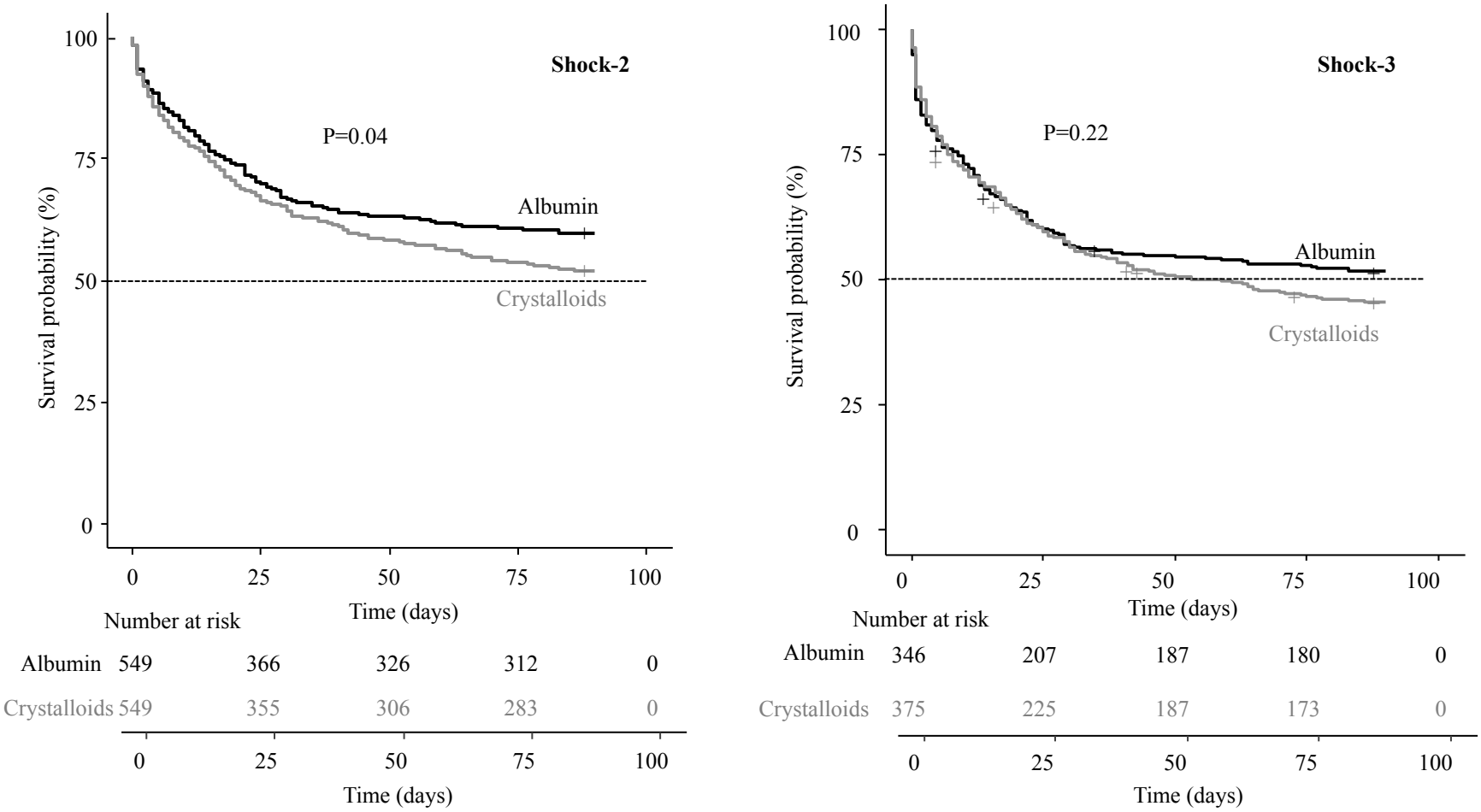
Shock-2
P=0.04
Albumin
Crystalloids
Survival probability (%)
100
75
50
25
0
0
25
50
75
100
Time (days)
Number at risk
Albumin 549 366 326 312 0
Crystalloids 549 355 306 283 0
Shock-3
P=0.22
Albumin
Crystalloids
Survival probability (%)
Time (days)
Number at risk
Albumin 346 207 187 180 0
Crystalloids 375 225 187 173 0

Table 2. Enrolment rate of septic shock patients in recent randomized controlled trials on sepsis (Sepsis-2 criteria).

Study	TRISS	SEPSISPAM	PROCESS	ARISE	ALBIOS	VASST
Patients enrolled (n)	1005	776	1341	1600	1135	778
Enrollment mid-date	2012	2011	2011	2011	2010	2003
Enrollment period (months)	25	22	74	66	42	57
Centers (n)	32	29	31	51	100	27
Enrollment rate (patients/month/center)	1.26	1.22	0.58	0.24	0.27	0.52
Enrollment rate (patients/month)	40,3	35,4	18	12	27	14