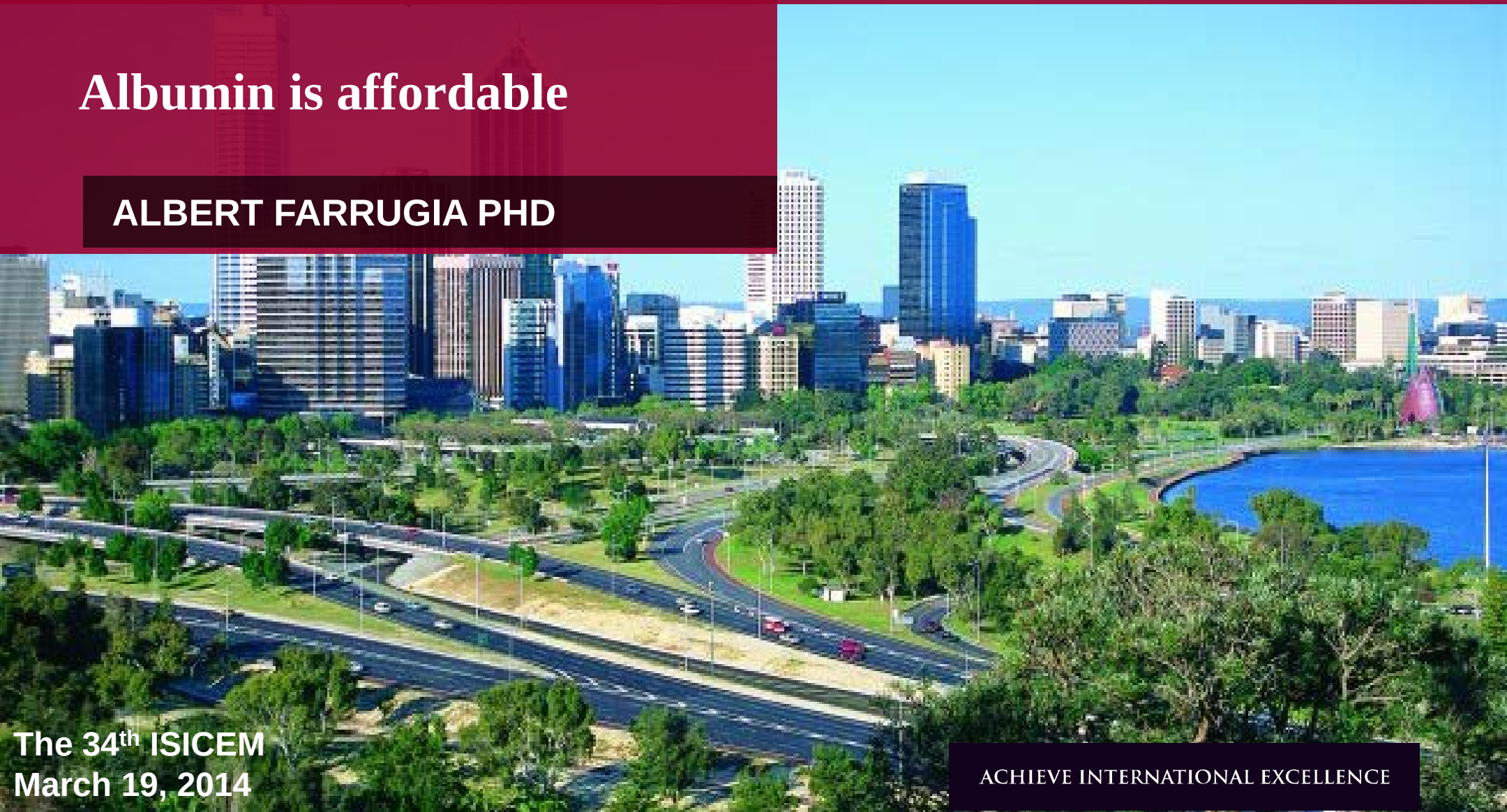
THE UNIVERSITY OF WESTERN AUSTRALIA

FACULTY OF MEDICINE, DENTISTRY AND HEALTH SCIENCES

Albumin is affordable

ALBERT FARRUGIA PHD



The 34th ISICEM
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ACHIEVE INTERNATIONAL EXCELLENCE

Disclosures

I provide services to the pharmaceutical and biotechnology industry, including the manufacturers of therapies described in this presentation, who are also major sponsors of this Symposium

Albumin Summary

- Albumin is an essential multifaceted natural protein
- A historical focus on its oncotic effects is being overtaken by an interest in other pharmacologic properties
- These allow hypotheses building in relation to certain disease states
- Clinical data in sepsis and cirrhosis indicates that these pharmacologic effects can lead to clinical benefit

But albumin is expensive !?!

VOLUVEN® CAN BE AN ALTERNATIVE TO HUMAN ALBUMIN

Used over 20 times more frequently than iso-oncotic albumin in Europe[7]

- Not blood derived—manufacturing unaffected by blood supply or shortages[9]
- No pharmacy tracking or special inventory procedures
- May help you achieve your conservation program goals
- Three-year shelf life
- No potential for viral contamination[9]
- Low potential for anaphylactic reactions (0.01% to 0.1%)[9]

Amounts to achieve similar volume expansion

Average price per mL[7]

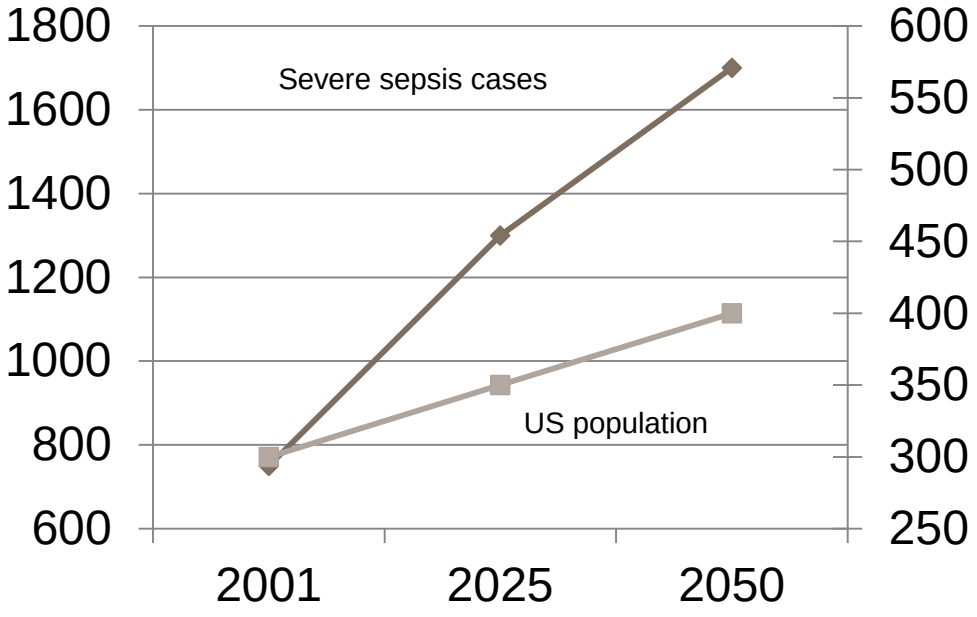
Product	Size	Average price/unit	Average price/mL
Albumin (5%)	250 mL	$38.29	$0.153
Albumin (5%)	500 mL	$73.34	$0.147
Voluven	500 mL	$43.49	$0.087

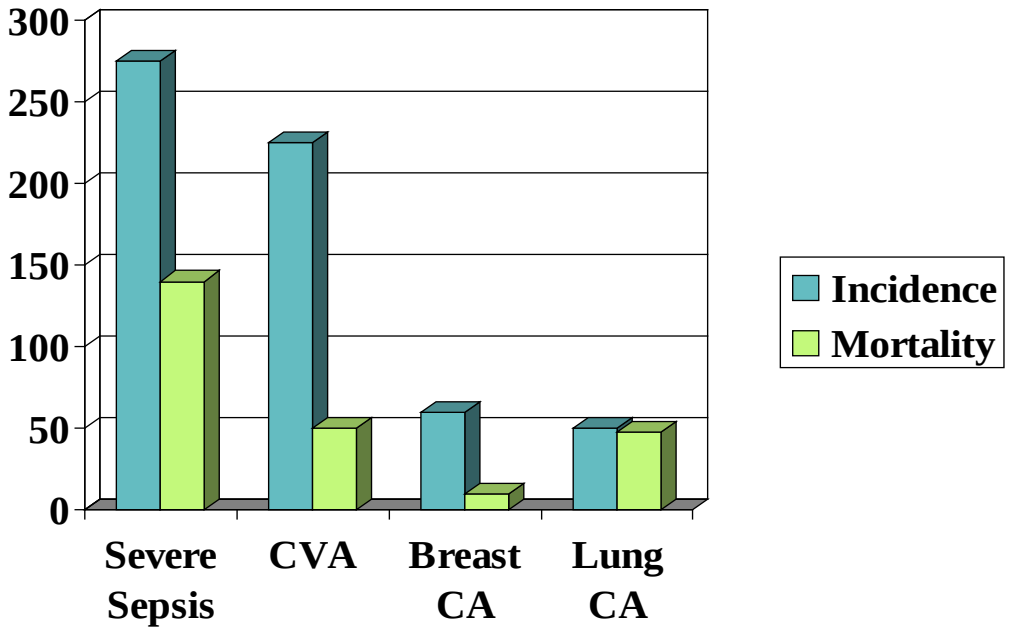
Voluven 41% to 43% less costly than albumin

IMS Health National Sales Perspective 4Q 2009.

Most common adverse reactions (incidence >1%) are pruritus, elevated serum amylase and hemodilution (resulting in dilution of blood components, e.g., coagulation factors and other plasma proteins, and in a decrease in hematocrit).

Severe Sepsis





- **More than 750,000 cases/Y of severe sepsis in US**
- **Estimated annual healthcare costs due to severe sepsis in U.S. exceed $16 billion**
- **Leading cause of death in non-coronary ICU**

Relative Survival Benefit and Morbidity with Fluids in Severe Sepsis - A Network Meta-Analysis of Alternative Therapies

M. Bansal[1], A. Farrugia[*,1,2], S. Balboni[1] and G. Martin[3]

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Abstract: *Background*: Fluid resuscitation is widely practiced in intensive care units for the treatment of sepsis. A comparison of the evidence base of different fluids may inform therapeutic choice.

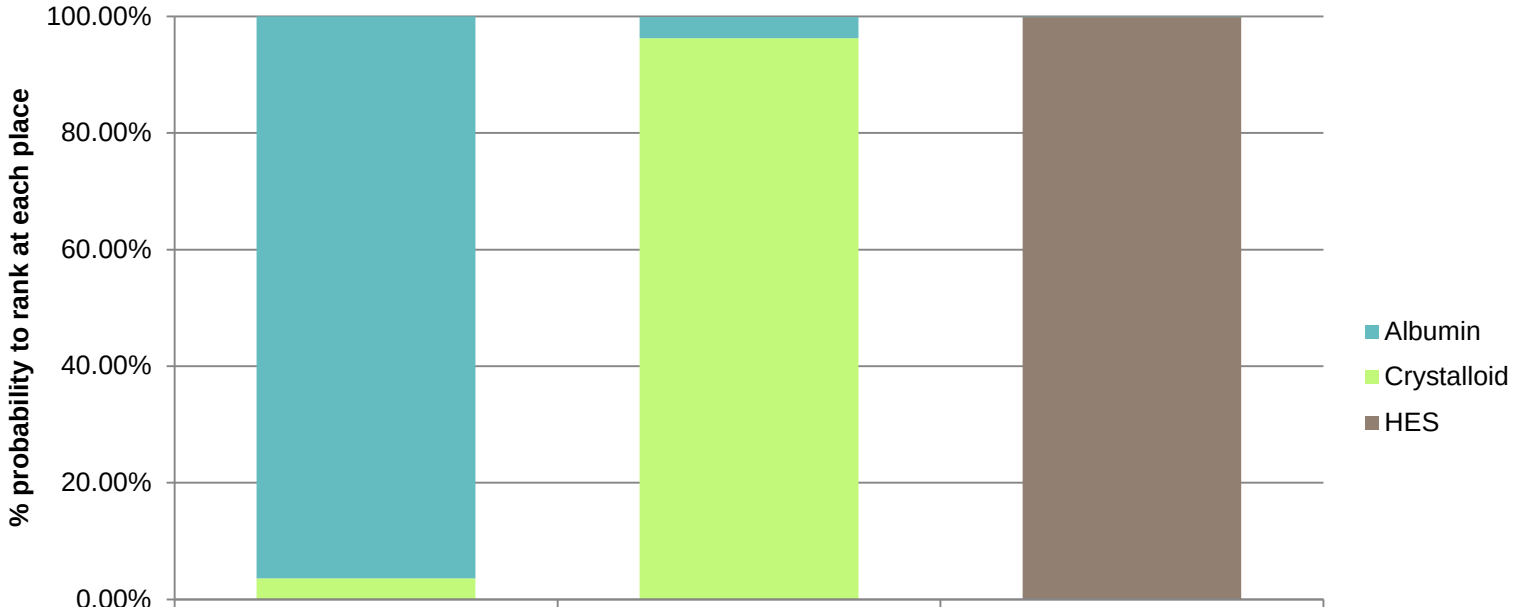
Methods: The risks of mortality and morbidity (the need for renal replacement therapies (RRT)) were assessed in patients with severe sepsis. A network meta-analysis compared trials for crystalloids, albumin and hydroxyethyl starch (HES). A literature search of human randomized clinical trials was conducted in databases, the bibliographies of other recent relevant systematic reviews and data reported at recent conferences. Mortality outcomes and RRT data with the longest follow up period were compared. A Bayesian network meta-analysis assessed the risk of mortality and a pair-wise meta-analysis assessed RRT using crystalloids as the reference treatment.

Results: 13 studies were identified. A fixed-effects meta-analysis of mortality data in the trials demonstrated an odds-ratio (OR) of 0.90 between crystalloids and albumin, 1.25 between crystalloids and HES and 1.40 between albumin and HES. The probability that albumin is associated with the highest survival was 96.4% followed by crystalloid at 3.6%, with a negligible probability for HES. Sub-group analyses demonstrated the robustness of this result to variations in fluid composition, study source and origin of septic shock. A random-effects pairwise comparison for the risk of RRT provided an OR of 1.52 favoring crystalloid over HES.

Conclusion: Fluid therapy with albumin was associated with the highest survival benefit. The higher morbidity with HES may affect mortality and requires consideration by prescribers.

***Current Drug Safety*, 2013, *8*, 236-245**

Network MA for studies in sepsis
Ranking probabilities of competing fluid treatments



	Rank 1	Rank 2	Rank 3
Albumin	96.38%	3.60%	0.00%
Crystalloid	3.61%	96.27%	0.00%
HES	0.01%	0.00%	99.87%

Choice of Fluids in Severe Septic Patients - A Cost-effectiveness Analysis Informed by Recent Clinical Trials

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Abstract: Fluid resuscitation with colloids is an established second line therapy for septic patients. Evidence of relative efficacy outcomes is tempered by considerations of the relative costs of the individual fluids. An assessment of recent large clinical trials was performed, resulting in a ranking in the efficacy of these therapies. Probabilities for mortality and the need for renal replacement therapy (RRT) were derived and used to inform a decision analysis model comparing the effect of crystalloid, albumin and hydroxyethyl starch solutions in severe septic patients followed from hospital admission to 90 days in intensive care. The US payer perspective was used. Model inputs for costs and efficacy were derived from the peer-reviewed literature, assuming that that all fluid preparations are bio-equivalent within each class of these therapies. Probabilities for mortality and the need for renal replacement therapy (RRT) data were synthesized using a Bayesian meta-analysis. Relative to crystalloid therapy, 0.21 life years were gained with albumin and 0.85 life years were lost with hydroxyethyl starch. One-way sensitivity analysis showed that the model's outcomes were sensitive to the cost of RRT but not to the costs of the actual fluids or any other costs. We conclude that albumin may be the most cost-effective treatment in these patients when the total medical costs and iatrogenic morbidities involved in treating sepsis with fluids are considered. These results should assist and inform decision making in the choice of these drugs.

Rev Recent Clin Trials. 2013 Dec 12. [Epub ahead of print] PMID: 24330133

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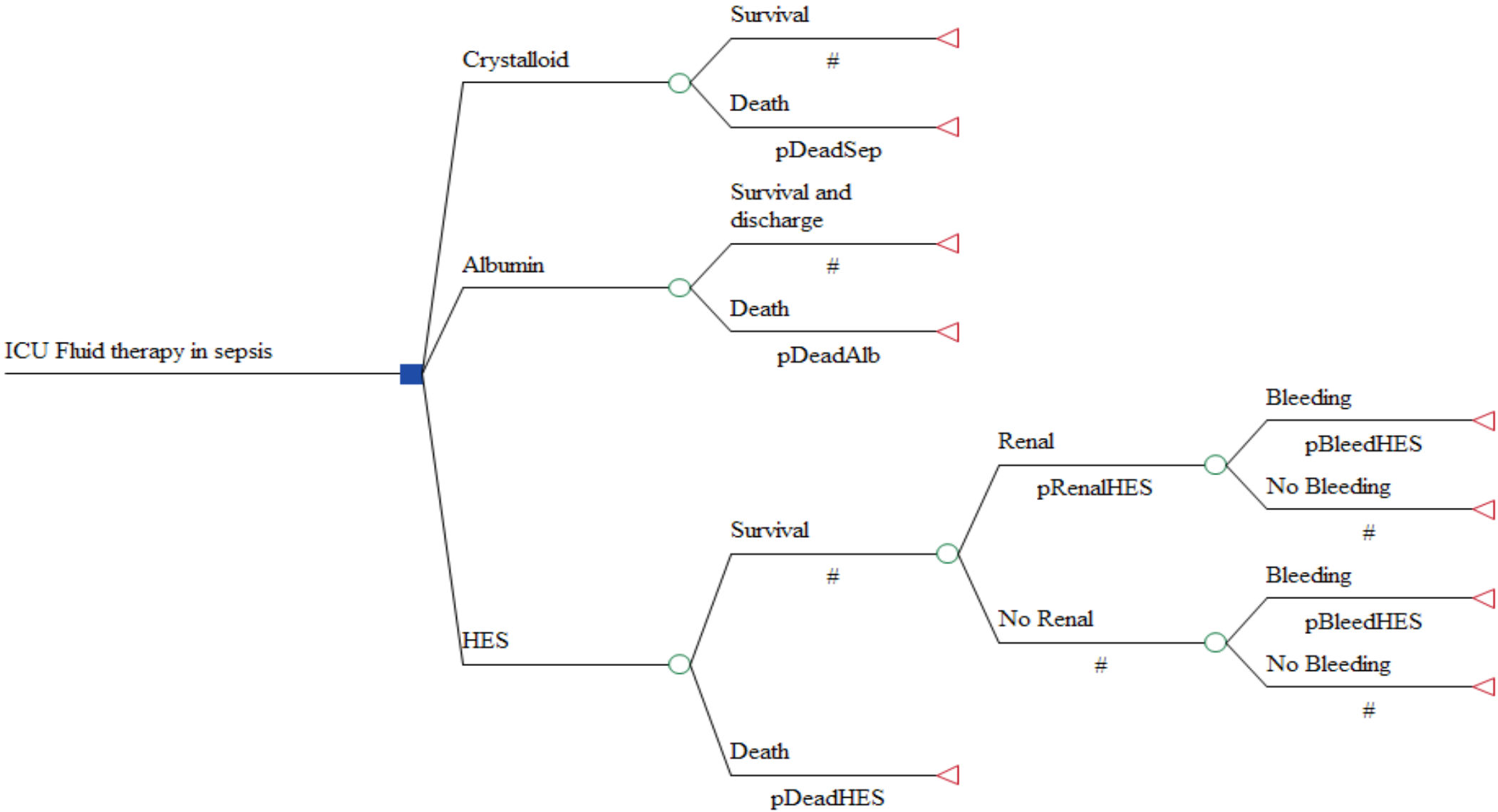
Decision tree to assess cost-effectiveness Fluids in sepsis



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Variables used to populate the decision analysis model

Variable (Abbreviation in the model)	Base case value	One-way sensitivity analysis values	Probability Distribution
Cost of albumin US$ (cAlb)	270	250 – 1,000	Not applied
Cost of hydroxyethyl starch US$ (cHES)	269	±20%	Not applied
Cost of sepsis standard of care US$ (cSepsisGen)	20,133	±20%	Gamma~ (55.56, 0.003)
Cost of renal replacement therapy US$ (cRenal)	142,404	76,540 – 30,616	Normal~ (142404, 146792)
Cost of treatment for bleeding US$ (cBleeding)	1,732	1,044 – 2,366	Normal~ (1732, 705.6)
Life expectancy – general population at 65 years (LEgenpop)	18.60	Not applied	Not applied
In-hospital or 28 day mortality with crystalloid (pDeadSep)	33.27%	Not applied	Beta~ (16.52, 33.14)
In-hospital or 28 day mortality with albumin (pDeadAlb)	30.95%	Not applied	Beta~ (14.78, 32.98)
In-hospital or 28 day mortality with hydroxyethyl starch (pDeadHES)	38.54%	Not applied	Beta~ (20.45, 32.60)
90-day excess mortality with hydroxyethyl starch (pDeadHES90)	13.6%	Not applied	Not applied
Excess probability of renal replacement therapy with hydroxyethyl starch (pRenalHES)	6.5%	3.5% - 19.5%	Uniform~(0.035, 0.195)
Excess probability of bleeding with hydroxyethyl starch (pBleeding)	3.29%	Not applied	Not applied
Prob. of mortality in bleeding episodes (pDeadBleed)	7.3%	Not applied	Beta~ (45.6, 579.1)
Prob. of mortality after RRT (pDeadRenal)	54.1%	50.8% - 60.8%	Uniform (0.508, 0.608)

Rev Recent Clin Trials. 2013 Dec 12. [Epub ahead of print] PMID: 24330133

Results of cost-effectiveness analysis

	Total Medical Cost	Effectiveness *
Crystalloid	$18,199	Reference
Albumin	$18,469	0.23
HES	$24,196	-0.45

* Years saved/lost compared to crystalloid.

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Results of One-way Sensitivity Analysis

Variable	Range ($)	Fluid Treatment	Total Cost/Life Year (Low) $	Total Cost/Life Year (High) $
Cost of Renal Replacement Therapy	76,540 – 306,160	Crystalloid	9,086	9,086
		Albumin	8,259	8,259
		Hydroxyethyl Starch	13,775	19,639
Cost of Albumin	250 – 1,000	Crystalloid	9,086	9,086
		Albumin	8,259	8,259
		Hydroxyethyl Starch	15,457	15,457
Cost of treatment of bleeds	1,193 – 2,693	Crystalloid	9,086	9,086
		Albumin	8,259	8,259
		Hydroxyethyl Starch	15,450	15,470

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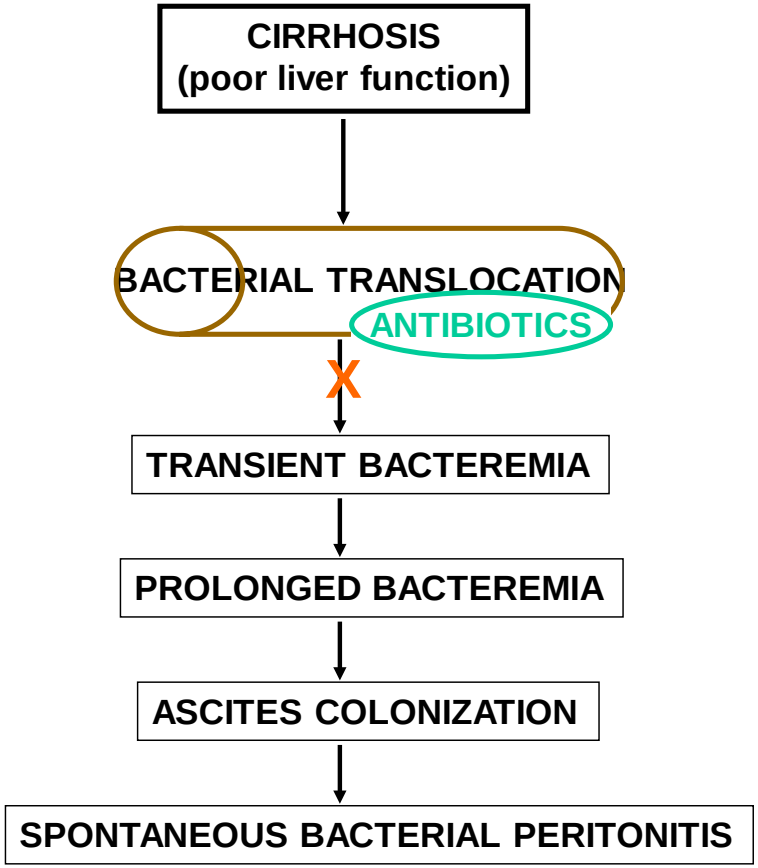
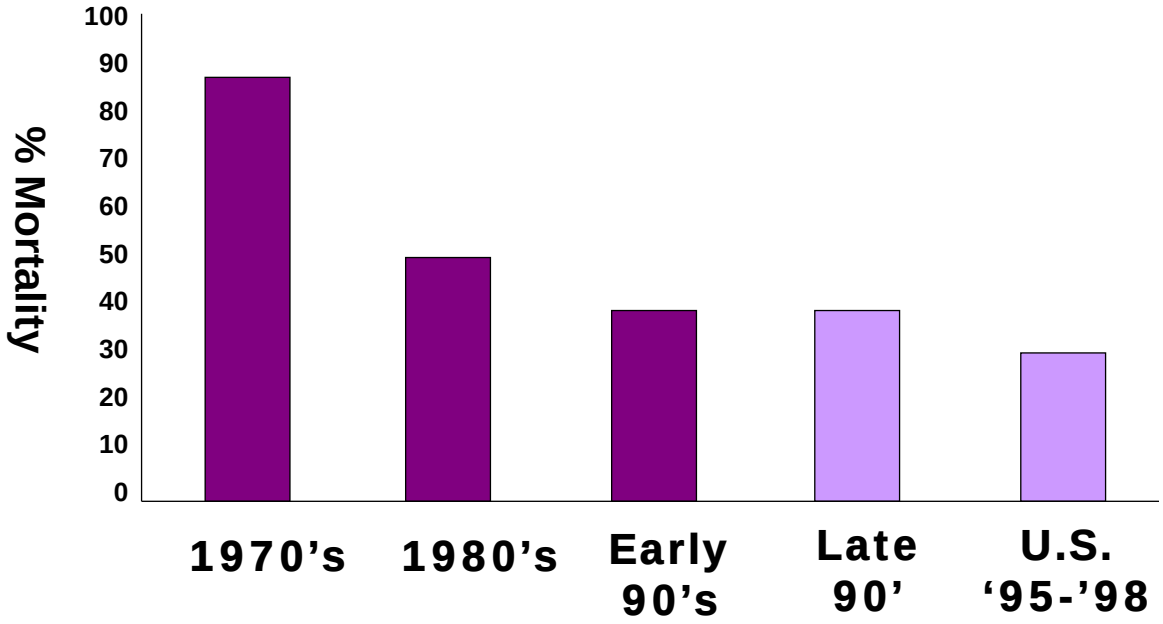
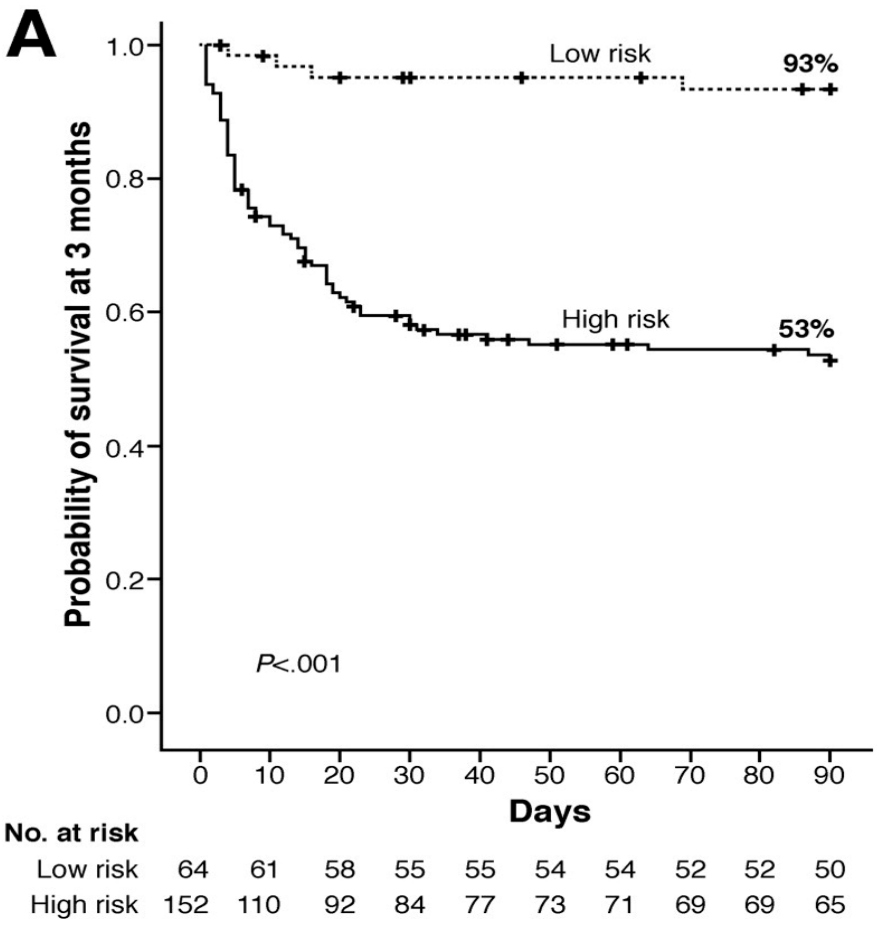
Spontaneous Bacterial Peritonitis

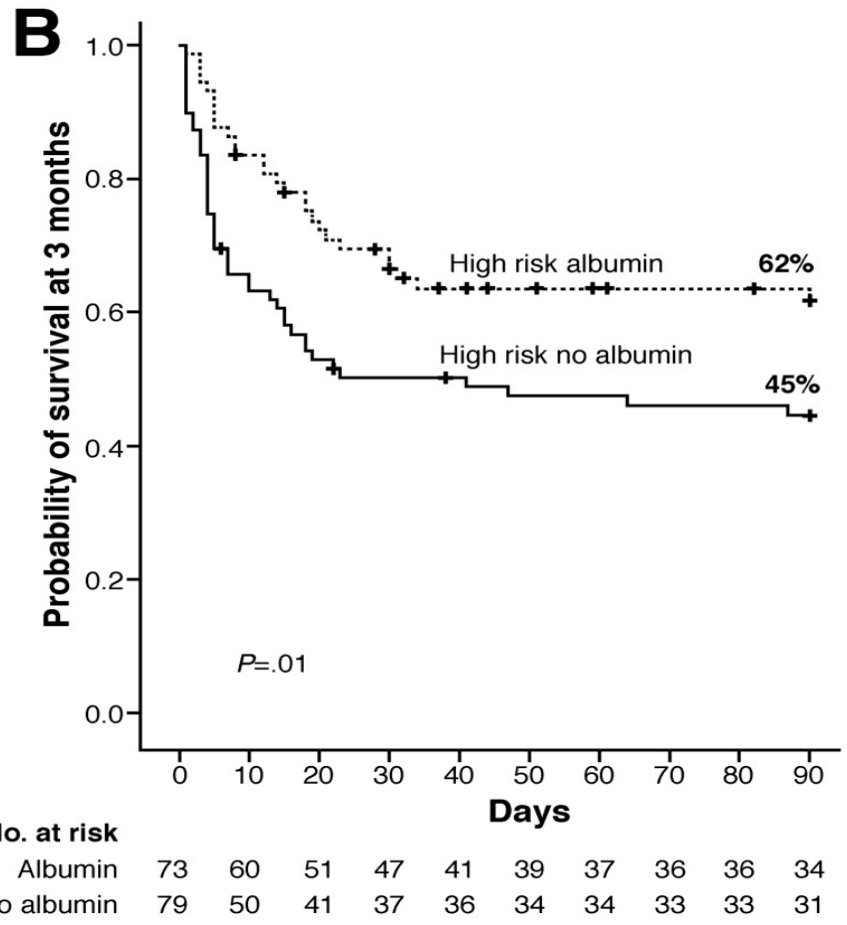


Mortality associated with SBP



Role of Albumin Treatment in Patients With Spontaneous Bacterial Peritoniti





Treatment of ascites with colloids
Incidence of liver-related complications

Type of complication	Albumin group* (*n*=30)	Polygeline group* (*n*=38)	Log-rank	Hazard ratio (95% CI)
Ascites episode	21 (70)	31 (82)	0.093	1.58 (0.91; 2.76)
Encephalopathy	7 (23)	9 (24)	0.385	1.56 (0.57; 4.25)
Hyponatraemia	5 (17)	11 (29)	0.110	2.33 (0.80; 6.76)
Renal impairment‡	4 (13)	8 (21)	–	–
Portal hypertensive bleeding‡	4 (13)	3 (8)	–	–
Bacterial infection‡				
Ascites	2 (7)	4 (11)	–	–
Other site†	1 (3)	6 (16)	–	–
Death	1 (3)	3 (8)	–	–

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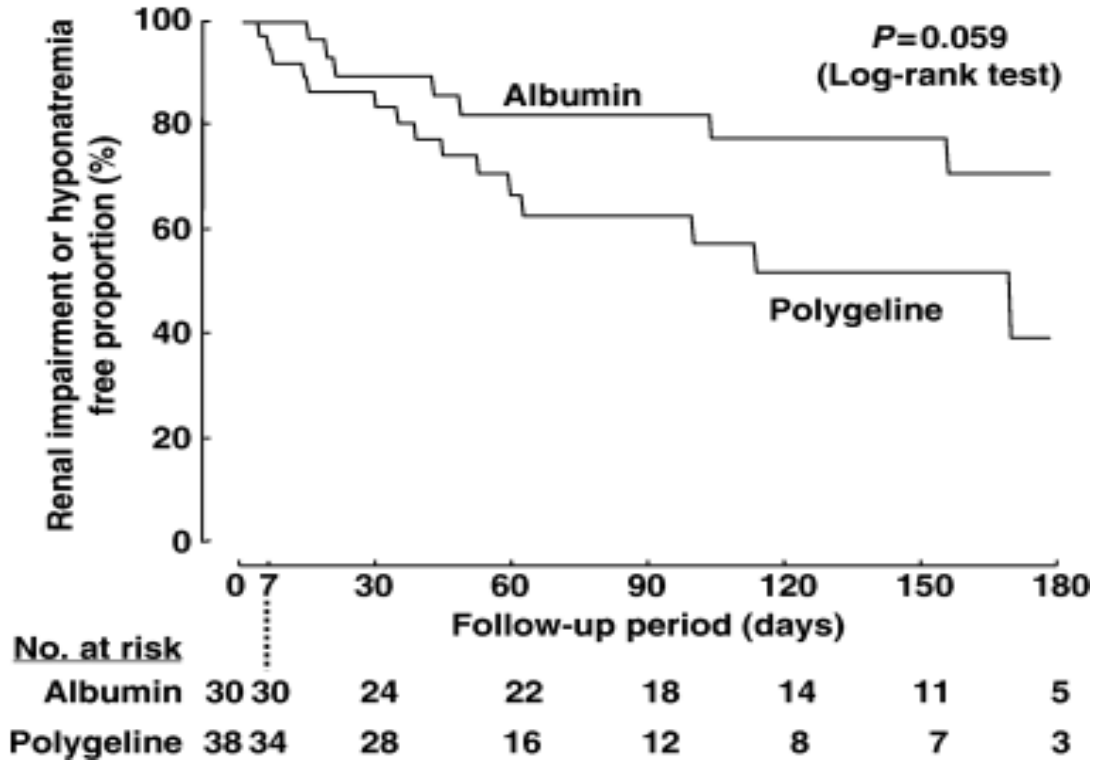
Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid



"…….the median total hospitalization-related cost over a 30-day period was lower in the albumin group than in the polygeline group (1915 vs. 4612 euros, respectively).

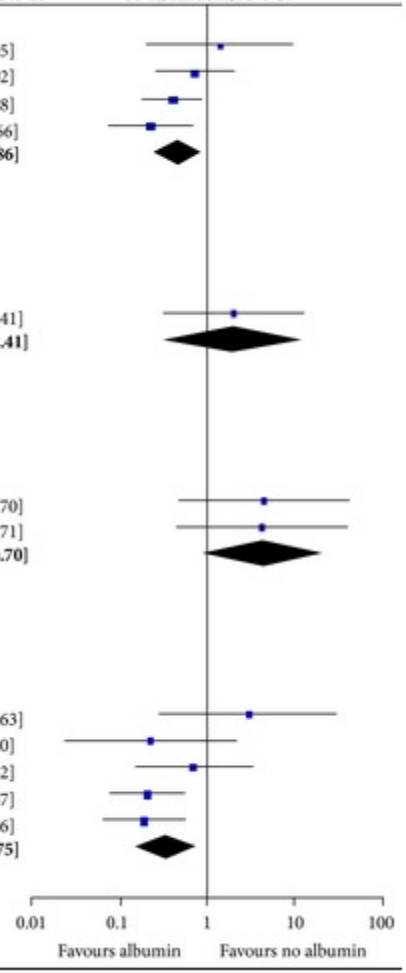
The difference in total costs between the two groups might be related to the difference in the incidence of liver-related complications requiring hospital care. These findings could have major implications for determining the real cost of treatment associated with albumin therapy.

Despite the lack of robust pharmacoeconomic data, treatment with albumin is often perceived as being much more expensive than treatment with a synthetic colloid because of the higher unit costs."

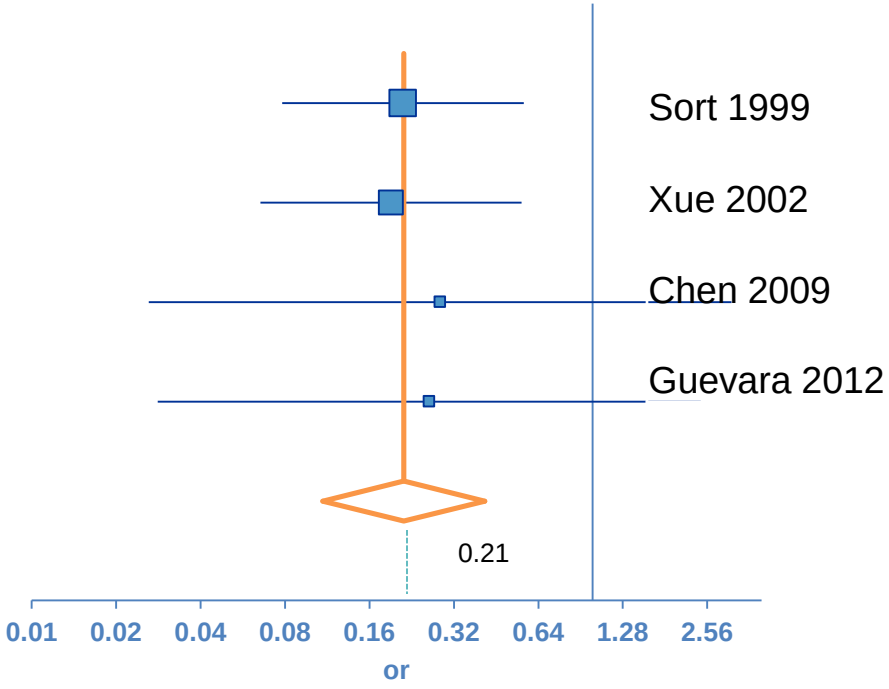
Cirrhotic patients with infections

Albumin versus no albumin

Study or subgroup	Albumin Events	Albumin Total	No albumin Events	No albumin Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Death						
Choi 2002	3	21	2	19	6.1%	1.42 [0.21, 9.55]
Guevara 2012	8	56	10	54	11.7%	0.73 [0.27, 2.02]
Sort 1999	14	63	26	63	13.8%	0.41 [0.19, 0.88]
Xue 2002	5	56	17	56	11.2%	0.22 [0.08, 0.66]
Subtotal (95% CI)		**196**		**192**	**42.9%**	**0.46 [0.25, 0.86]**
Total events	30		55			
Heterogeneity: $\tau^2 = 0.09$; $\chi^2 = 3.93$, df = 3 ($P = 0.27$); $I^2 = 24\%$						
Test for overall effect: $Z = 2.46$ ($P = 0.01$)						
1.1.2 Hyponatraemia						
Choi 2002	4	21	2	19	6.5%	2.00 [0.32, 12.41]
Subtotal (95% CI)		**21**		**19**	**6.5%**	**2.00 [0.32, 12.41]**
Total events	4		2			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 0.74$ ($P = 0.46$)						
1.1.3 Infection resolution						
Nazar 2009	55	56	50	54	4.9%	4.40 [0.48, 40.70]
Sort 1999	62	63	59	63	5.0%	4.20 [0.46, 38.71]
Subtotal (95% CI)		**119**		**117**	**9.9%**	**4.30 [0.89, 20.70]**
Total events	117		109			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, df = 1 ($P = 0.98$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.82$ ($P = 0.07$)						
1.1.4 Renal impairment						
Choi 2002	3	21	1	19	4.5%	3.00 [0.28, 31.63]
Guevara 2012	1	56	4	54	4.9%	0.23 [0.02, 2.10]
Nazar 2009	3	56	4	54	8.0%	0.71 [0.15, 3.32]
Sort 1999	6	63	21	63	12.0%	0.21 [0.08, 0.57]
Xue 2002	5	56	19	56	11.3%	0.19 [0.07, 0.56]
Subtotal (95% CI)		**252**		**246**	**40.7%**	**0.34 [0.15, 0.75]**
Total events	18		49			
Heterogeneity: $\tau^2 = 0.28$; $\chi^2 = 6.09$, df = 4 ($P = 0.19$); $I^2 = 34\%$						
Test for overall effect: $Z = 2.65$ ($P = 0.008$)						

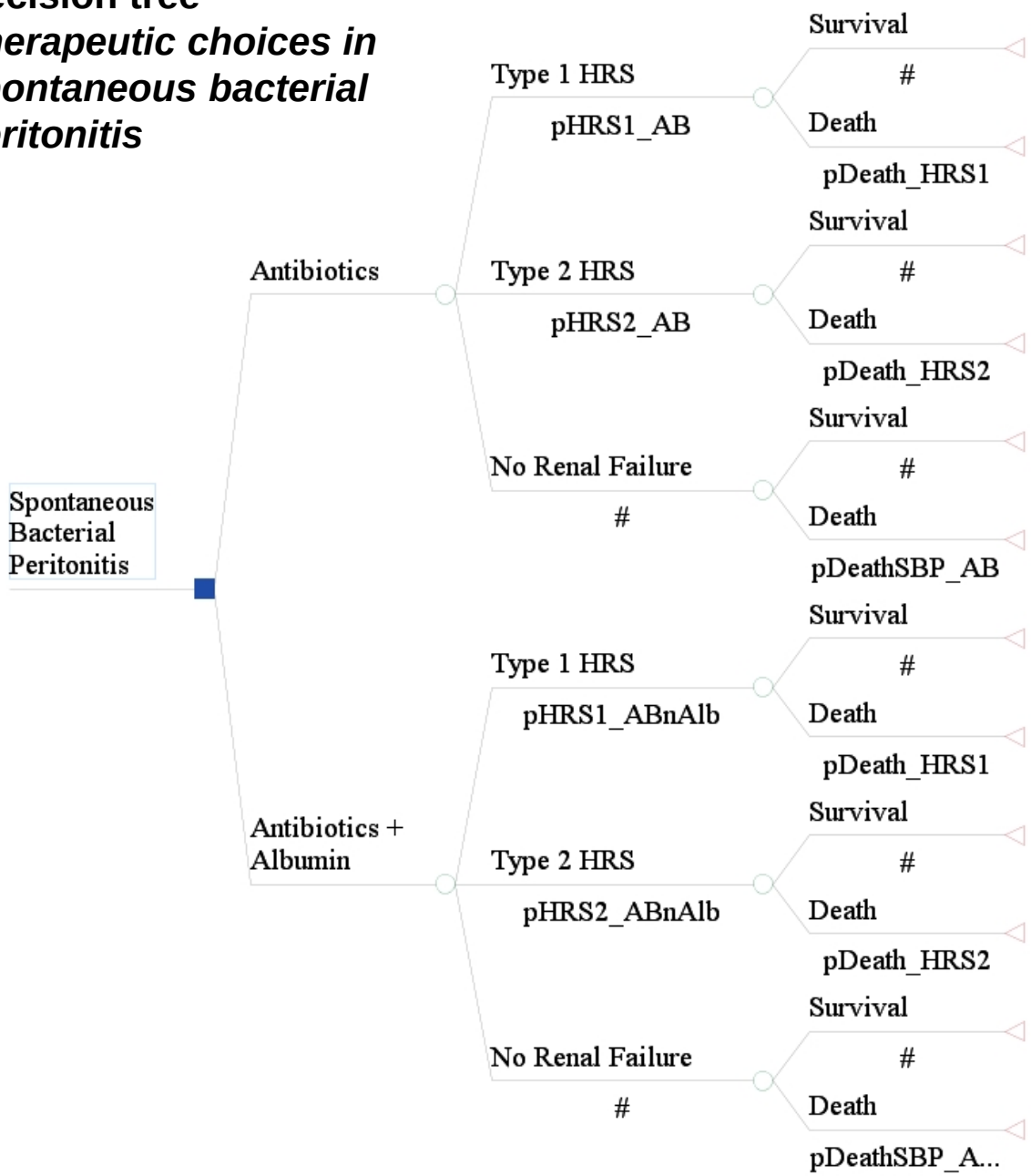


Meta Anayses – Albumin in SBP



Decision tree

Therapeutic choices in spontaneous bacterial peritonitis



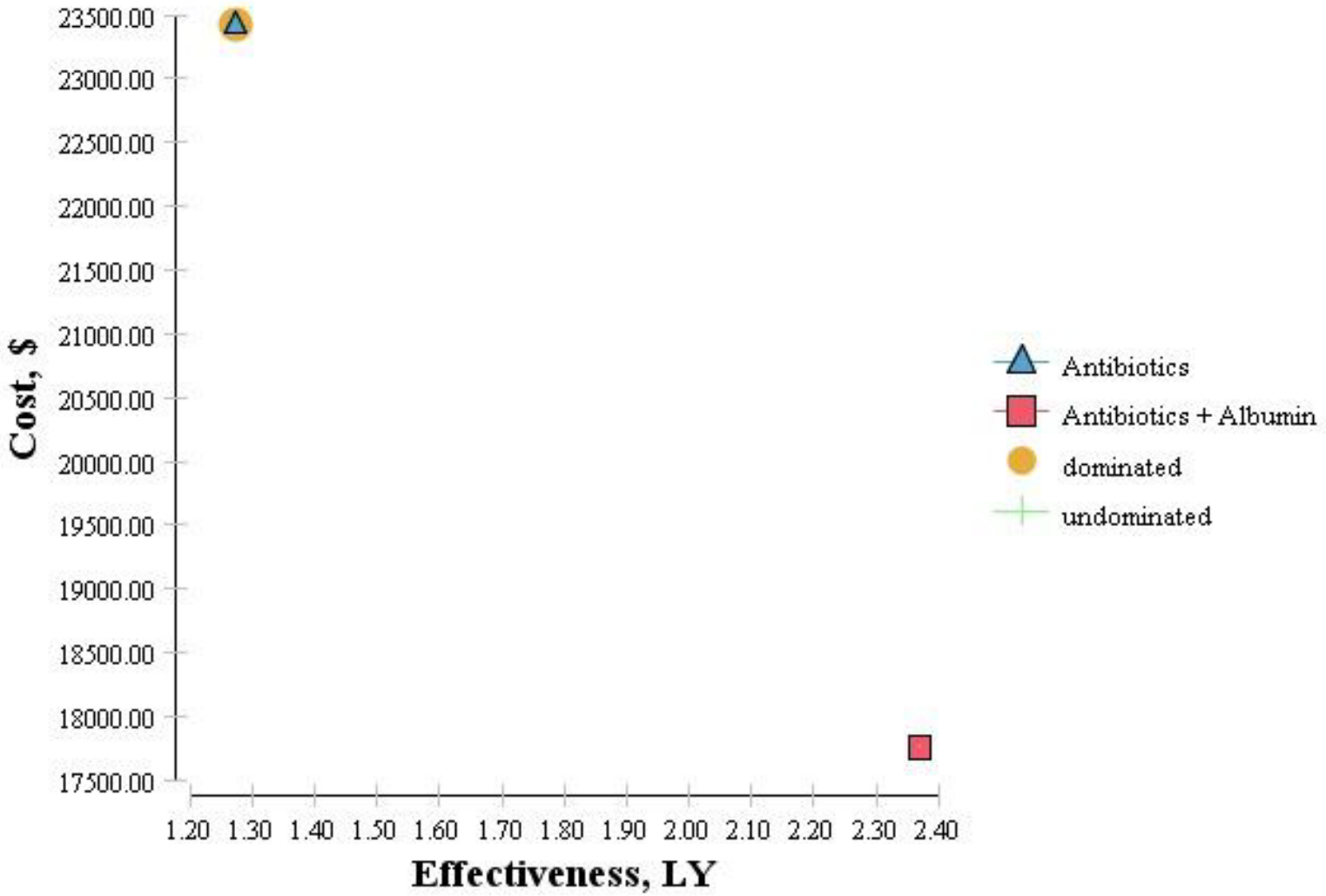
Variables in SBP cost-effectiveness model

Name	Description	Formula	Value	Comment
LEgenpop	Life expectancy in general population at 56 yrs	26.35	26.35	Average age of SBP according to HCUP 2011 is 56 yrs. Life expectancy of ((26.8+25.9)/2) obtained from CDC 2008
Probabilties				
pDeath_Renal_AB	Probability of mortality in renal impairment with antibiotics	13/63	20.60%	Sort 1999 table 2 footnote
pDeath_Renal_ABnAlb	Probability of mortality in renal failure with albumin and antibiotics	5/63	7.90%	Sort 1999 table 2 footnote
pDeathSBP_AB	Probability of in-hospital mortality due to other causes (not renal) in SBP with antibiotics	(18-13)/63	7.94%	Sort 1999 table 2 footnote Derived figure consistent with HCUPnet 2011 SBP mortality data (6.78%)
pDeathSBP_ABnAlb	Probability of in-hosp mortality due to other causes (not renal) in SBP with antibiotics and albumin	(6-5)/63	1.59%	Sort 1999 table 2 footnote
pHRS_AB	Probability of HRS with antibiotics	0.08	8.00%	Gines 2003 Pg1823 1st col, 3rd para.
pHRS_ABnAlb	Probability of HRS with antibiotics and albumin	(.10/.33)*0.08	2.42%	used 8% from Gines 2003 pg1823 1st col, 3rd para and derived from proportion of renal impairment with antibiotics to antibio+albumin from Sort 1999
pRenal_AB	Probability of Renal failure with antibiotics	0.33	33.00%	Sort 1999 table 2
pRenal_ABnAlb	Probability of Renal failure with antibiotics and albumin	0.1	10.00%	Sort 1999 table 2
Costs				
cAlb	Cost of albumin	270	270	Check???
cHRS	Cost of treating hepatorenal syndrome (8.6 days)	22341	22341	HCUPnet 2011 (US) conversion to 2014 prices needed Cost of hospital stay +Trelipressin and albumin (Gines 2003 for dose), prices tbd for EU Hosital days from HCUPnet
cRenal	Cost of treating/managing renal failure (3.9 days)	7060	7060	HCUP 2011 ICD9 code: 586. (se: 682) Inflated to 2013 CPI for Medical Care Hosital days from HCUPnet 2013: 422.83 2011: 400.26 6683*(422.83/400.26) = 7060 Length of stay = 3.9 days
cSBP	Cost of treating spontaneous bacterial peritonitis (7 days)	15604	15604	HCUP 2011 ICD9 code: 567.23. (se= 912) Inflated to 2013 CPI for Medical Care. Hospital days from HCUPnet 2013: 422.83 2011: 400.26 14771*(422.83/400.26) = 15,604 Length of stay = 7.0 days

Albumin in sepsis
Mortality and differential in lives saved and life years gained

Database	Hospital mortality	Patients alive at discharge	Lives saved with albumin	DEALE	Total survival years	Life years gained with albumin
Without albumin	53.7%	5156	513	9.78	50426	5017
With albumin	49.1%	5669		9.78	55443	

Outcomes of cost-effectiveness model Albumin in SBP



Summary

- In the current era of cost-containment the total medical costs of treatment are important
- Hence, individual therapy costs are secondary as long as they make the overall treatment more cost effective
- Albumin's pharmacological properties are lending themselves to indications other than the historical use as a volume expander
- Two particular areas, sepsis and cirrhosis, are increasingly supported by evidence and guidelines
- Pharmacoeconomic modeling shows that in these conditions, albumin is a cost-effective treatment