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.

Keywords: Clinical trials, colloids, costs, decision analysis, fluid therapies, sepsis.

INTRODUCTION

Severe sepsis is a clinical syndrome, originating in the systemic inflammatory response following infection, which leads to organ dysfunction, and is a major cause of hospital mortality and a considerable economic burden [1]. Resuscitation in sepsis is initially based on fluid therapy, through guidelines by the Surviving Sepsis Campaign [1]. This modality remains controversial [2] and is an active area of clinical investigation [3] The relative proportion of the different fluids used in sepsis varies between countries [4]. Cost is invariably mentioned as a factor in guidelines on the choice of fluids [5].

Treating hypovolemia ensuing from sepsis is the basis for early patient resuscitation. Despite the increased microvascular permeability characterizing sepsis [1], plasma volume is expanded in septic patients given albumin [6] and hypoalbuminaemia is corrected. Albumin's repertoire of molecular functions includes antioxidant properties that are sustained in septic patients, which is another possible therapeutic feature [7]. A subgroup analysis of a major intensive care fluid therapy trial has indicated a survival benefit for septic patients given albumin [8], a finding supported by a meta-analysis of this and other trials [9]. This has contributed to a number of reported [10] and ongoing [11,12] trials for albumin in sepsis.

Hydroxyethyl starches (HES) are a class of colloid solutions that have been used in a range of clinical applications requiring colloid therapy. Their lower cost per unit compared to albumin has been the main driver for their adoption in clinical practice. HES has been supplied in successive generations of products over the past thirty years, and manufacturers have attempted to develop molecules that do not lead to the adverse events that have been associated with these products from their inception. The most serious of these include bleeding and renal problems [13]. Over the past decade, a number of hydroxyethyl starch products with an average molecular weight of 130 kD and a degree of substitution of 0.4 (low molecular weight (LMW) hydroxyethyl starch) have been introduced into therapeutic practice. These properties are claimed to ameliorate or obviate the haemostatic and renal adverse events [14]. Recent meta-analyses do not support these claims [15,16], and have led authorities in the United States and Europe to place restrictions on the use of these drugs.

Given the importance of including all healthcare repercussions in providing choices in therapeutics, and the uncertainties in many of the aspects of fluid therapy discussed above, an analysis of recent clinical trials was used to inform a decision analysis model comparing the cost-effectiveness of crystalloid, albumin and hydroxyethyl starch in the specific area of severe sepsis. The role of such models in decision making in sepsis has included the use of early goal directed therapy [17].

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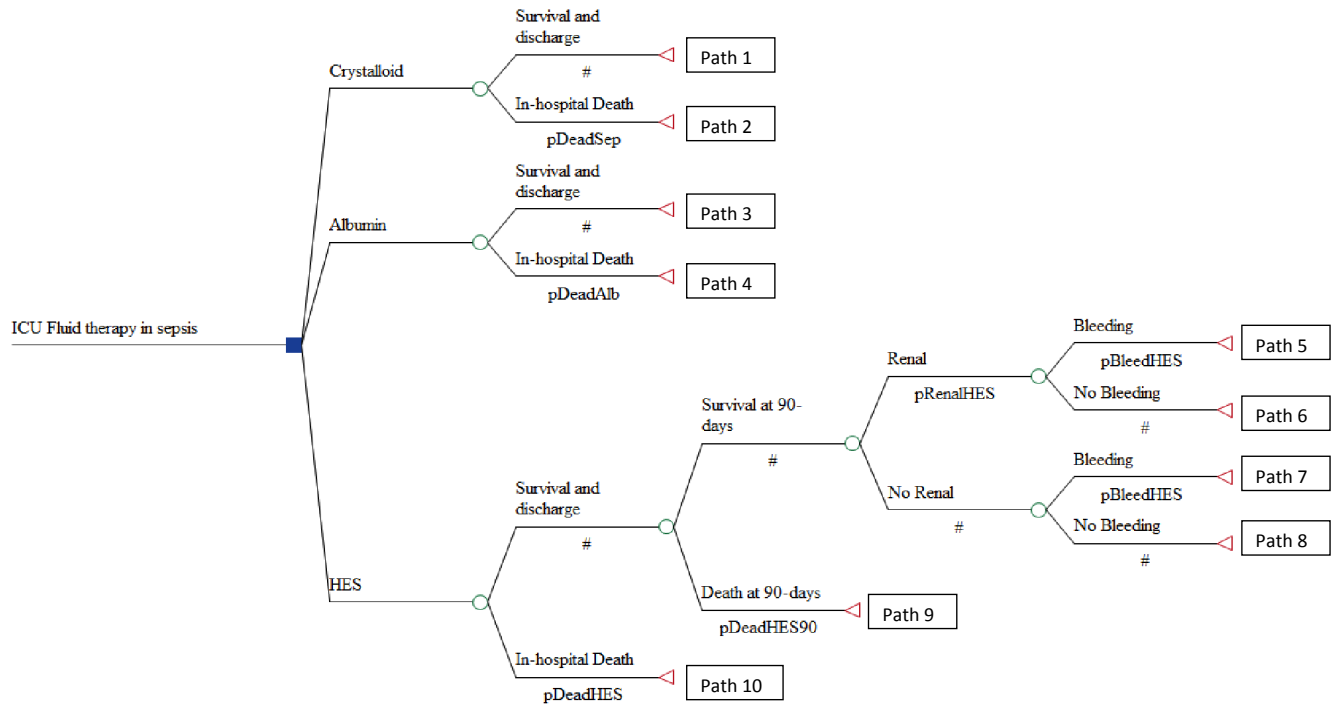
Fig. (1). Structure of the Decision Analysis model comparing costs and effectiveness of crystalloid, albumin and hydroxyethyl starch (HES) using outcomes of mortality, renal replacement therapy and bleeding. The payoffs for each path are shown in (Table **2**).

MATERIALS AND METHODS

The fluids were the most commonly used in critical care, as assessed by international surveys [4]. As previously described[18], a literature search for randomized clinical trials of fluid therapy in severe sepsis were used to generate a network meta-analysis (NMA) allowing the calculation of probabilities of survival and morbidity for the different therapies. Since the initial study, a further clinical trial comparing fluid treatments in critically ill patients has been published, which includes subsets of patients receiving HES, crystalloids and albumin [19], and which has been included in the NMA and the subsequent calculations for the cost-analysis. As CRISTAL is the only study reporting 90 day mortality for albumin, it was not reasonable to use the data for 90 day mortality from the NMA and hence only the 28 day mortality data for albumin, and crystalloid in sepsis patients was included from the CRISTAL study (see discussion).

CLASS=SECTION3> DECISION ANALYSIS MODEL

A software package – TreeAge Pro 2012 (TreeAge Software, Inc. 12.1.2; Williamstown, MA,) - was used to construct the decision tree considering a hypothetical patient population with severe sepsis treated with crystalloid, albumin or hydroxyethyl starch at the initial decision node (Fig. **1**). The patients were followed from hospital admission up to 90-days. The model was applied to third party payers in the US.

Each treatment arm had a chance node specifying in-hospital survival. HES had additional 90-day mortality as was estimated by network meta-analysis [20]. Patients treated with albumin and crystalloids were assumed to have no iatrogenic morbidities [8] [see discussion], whereas patients treated with hydroxyethyl starch were assigned a prob-

ability of morbidities ensuing in the form of need for renal replacement therapy (RRT) and hemostatic dysfunction. RRT and hemostatic dysfunction were associated with further mortality in patients using HES [21,22].

The life years for effectiveness were calculated using the Declining Exponential Average Life Expectancy (DEALE) [23]. All the costs and effectiveness pay-offs at terminal node are shown in (Table **2**). A cost of US $10,000 per life year gained was arbitrarily assigned as the threshold at which a treatment was considered to be cost-effective[24]. Each chance node assigned with a probability is described in detail below.

MODEL INPUTS

(Table **1**) summarizes the variables used to populate the decision tree.

Mortality

Odds ratios (ORs) derived from the NMA [20] were converted to probabilities [25] (shown below) of mortality with albumin and HES, using data for in-hospital deaths for patients with severe sepsis obtained from the Healthcare Cost and Utilization project (HCUPnet) [22]. The HCUPnet is an online database of inpatient and emergency department utilization with information classified by International Classification of Diseases (ICD) codes and other identifiers. The statistics in the HCUPnet are usually for the standard of care of a disease and not classified by treatments used in a disease. We assumed that the fluid used for the current standard of care for patients with severe sepsis in the HCUPnet was crystalloid, on the basis of market research on fluid use in septic patients [26] as well as on clinical guidelines [1].

$P(in-hospital\ mortality\ with\ albumin)$

$$= \frac{OR\ (in-hospital\ mortality\ ,crystalloid\ vs.albumin) * \frac{P(in-hospital\ mortality\ with\ crystalloid)}{1-P(in-hospital\ mortality\ with\ crystalloid)}}{1 + [OR\ (in-hospital\ mortality\ ,crystalloid\ vs.albumin) * \frac{P(in-hospital\ mortality\ with\ crystalloid)}{1-P(in-hospital\ mortality\ with\ crystalloid)}]}$$

$P(in-hospital\ mortality\ with\ HES)$

$$= \frac{OR\ (in-hospital\ mortality,crystalloid\ vs.\ HES) * \frac{P\ (in-hospital\ mortality\ with\ crystalloid)}{1-P(in-hospital\ mortality\ with\ crystalloid)}}{1 + [OR\ (in-hospital\ mortality,crystalloid\ vs.\ HES) * \frac{P\ (in-hospital\ mortality\ with\ crystalloid)}{1-P(in-hospital\ mortality\ with\ crystalloid)}]}$$

$P(90-day\ mortality\ with\ HES)$

$$= \frac{OR\ (90-day\ mortality,crystalloid\ vs.\ HES) * \frac{P\ (post\ discharge\ mortality\ with\ crystalloid)}{1-P(post\ discharge\ mortality\ with\ crystalloid)}}{1 + [OR\ (90-day\ mortality,crystalloid\ vs.\ HES) * \frac{P\ (post\ discharge\ mortality\ with\ crystalloid)}{1-P(post\ discharge\ mortality\ with\ crystalloid)}]}$$

Probabilities of mortality associated with iatrogenic (excess relative to standard treatment) cases of RRT and bleeding with HES were used from different sources. Probability of mortality after RRT was taken from a prospective multi-center observational study among critically ill patients [21]. The HCUPnet provided the in-hospital deaths for bleeding episodes (ICD 9 code: 459.0). These co-morbidity related mortality data were not reported in the trials as we tried to source all the values of the parameters from a single source or method.

Excess Morbidities Associated with HES

Morbidities included the need for RRT and bleeding, which are complications of severe sepsis irrespective of the type of fluid resuscitation but the relative incidence of these complications increases with HES [13]. The Bayesian pair-wise direct meta-analysis [20] of a subset of trials for patients in need of RRT was used to calculate an odds-ratio for this event, which was converted to the probability (shown below) of the need for RRT [25]. We calculated the excess probability (difference of the relevant probabilities between control and treatment) relative to the need for RRT in septic patients on current standard of care, using the figure of 16% from Adrie *et al.* [27] (Table **1**).

The excess probability of bleeding with hydroxyethyl starch was the difference between probabilities of hydroxyethyl starch and control fluid treatment arms in the trial reported by Perner *et al.* [28]. The data was obtained from this trial because this was the only large trial which reported data on bleeding.

Cost Inputs

All the costs were inflated to 2012 costs using consumer price index (CPI) of the year 2012 for medical care. Since

the costs were calculated for a time period of less than a year, no discount rates were utilized. The cost of treating severe sepsis under standard of care was taken from the 2010 HCUPnet total cost data [22]. This cost of standard of care was assumed to include cost of crystalloid, treatment of complications in severe sepsis and hospital use under standard of care. The cost of albumin was added to this cost to show the cost of treatment with albumin.

The costs of albumin and HES were obtained from an analysis published by the Market Research Bureau (MRB) [26] for 2010. The doses used in sepsis patients were estimated from published studies in Australasia and Germany, respectively, [4,29] in the absence of comparable data from the USA. We added the cost of treating the excess complications along with hospital use and drug cost to the total cost of treatment under HES.

Continuous renal replacement therapy (CRRT) is considered to be the first line treatment in patients with sepsis requiring renal support [30] and the cost was obtained from Rauf *et al.* [31]. The level of transfusion support for patients on HES resuscitation in severe sepsis was obtained from the VISEP [32] trial, which is the only study quantifying this therapy, costed by Shander *et al.* [33].

Life Expectancy Estimates – Effectiveness

These were extracted from the model by performing Declining Exponential Average Life Expectancy DEALE calculations [23] for septic patients undergoing standard care (crystalloid) as well as undergoing albumin or hydroxyethyl starch therapy. DEALE calculates patient specific life expectancy [23] using mortality rates in the general population and in the disease-specific population.

Table 1. Variables used to Populate the Decision Analysis Model.

Variable (Abbreviation in the Model)	Base Case Value	One-way Sensitivity Analysis Values	Probability Distribution	Notes, Assumptions and Sources
Cost of albumin US$ (cAlb)	270	250 – 1,000	Not applied	Based on dose from SAFE sepsis sub group [4] converted into 5% albumin units priced at $71 each [26]. One-way sensitivity value assumed.
Cost of hydroxyethyl starch US$ (cHES)	269	±20%	Not applied	Based on dose from Bayer *et al.* [29] converted into total of six 500 ml units at $45 each [26]. One-way sensitivity value assumed.
Cost of sepsis standard of care US$ (cSepsisGen)	20,133	±20%	Gamma~ (55.56, 0.003)	2010 costs ($17,008) for severe sepsis related to ICD-9 code: 995.92." in HCUP 2010 [22]. One-way sensitivity value assumed and standard error ($2,251) from HCUP 2010 [22]. Inflated to 2012 costs (http://www.bls.gov/data/).
Cost of renal replacement therapy US$ (cRenal)	142,404	76,540 – 306,160	Normal~ (142404, 146792)	From cost of CRRT in Rauf *et al.* [31] One – way sensitivity value and standard deviation ($122,327) from Rauf *et al.* [31] Inflated to 2012 cost (http://www.bls.gov/data/).
Cost of treatment for bleeding US$ (cBleeding)	1,732	1,044 – 2,366	Normal~ (1732, 705.6)	VISEP trial reports septic patients on hydroxyethyl starch required two more red cells than controls [32] which Shander *et al.* report mean cost US$ 761 each [33]. One- way sensitivity value and standard deviation ($294 x 2) from Shander *et al.* Inflated to 2012 cost (http://www.bls.gov/data/).
Life expectancy – general population at 65 years (LEgenpop)	18.60	Not applied	Not applied	Extracted from Life Expectancy table at CDC. The life expectancy was used to calculate life expectancy in various disease states using DEALE [23].
In-hospital or 28 day mortality with crystalloid (pDeadSep)	33.27%	Not applied	Beta~ (16.52, 33.14)	Extracted from severe sepsis related to ICD-9 code: 995.92 in HCUP [22] (See Model Inputs section). Standard error (6.62%) from HCUP 2010 [22].
In-hospital or 28 day mortality with albumin (pDeadAlb)	31.2%	Not applied	Beta~ (14.97, 33.01)	Extracted from the network meta-analysis with colloids (hydroxyethyl starch or albumin) vs. crystalloid trials on patients with sepsis and mortality as an outcome (See Model Inputs section). Standard error with crystalloid (6.62%) from HCUP 2010 [22] assumed.
In-hospital or 28 day mortality with hydroxyethyl starch (pDeadHES)	35.8%	Not applied	Beta~ (18.41, 33.02)	Extracted from the network meta-analysis with colloids (hydroxyethyl starch or albumin) vs. crystalloid trials on patients with sepsis and mortality as an outcome (See Model Inputs section). Standard error with crystalloid (6.62%) from HCUP 2010 [22] assumed.
90-day excess mortality with hydroxyethyl starch (pDeadHES90)	12.1%	Not applied	Not applied	Derived from crystalloid 90-day mortality data in 6S trial [28] and odds ratio at 90 days from meta-analysis (See Model Inputs section).
Excess probability of renal replacement therapy with hydroxyethyl starch (pRenalHES)	6.5%	3.5% - 19.5%	Uniform~(0.035, 0.195)	This is derived from the difference of control and hydroxyethyl starch. The base rate for crystalloid is 16% from Adrie 2005 (Table **3**) [27]. 22.5% (for HES) is extracted from the meta-analysis (direct comparison) of RRT outcomes in hydroxyethyl starch vs. crystalloid trials on patients with severe sepsis. 3% - 26% (for crystalloid) depending on the infection site for one way sensitivity analysis.

Table 1. Contd....

Variable (Abbreviation in the Model)	Base Case Value	One-way Sensitivity Analysis Values	Probability Distribution	Notes, Assumptions and Sources
Excess probability of bleeding with hydroxyethyl starch (pBleeding)	3.29%	Not applied	Not applied	Difference between hydroxyethyl starch and control groups in 6S trial [28]
Prob. of mortality in bleeding episodes (pDeadBleed)	7.3%	Not applied	Beta~ (45.6, 579.1)	In-hospital deaths from HCUP 2010 ICD 9: 459.0 [22]. Standard error (1.04%) from HCUP 2010 [22]
Prob. of mortality after RRT (pDeadRenal)	54.1%	50.8% - 60.8%	Uniform (0.508, 0.608)	Vesconi 2009 (Table **1**) [21]. Sensitivity values from Vesconi (Table **2**) [21] for less intensive (50.8%) and more-intensive doses (60.8%)

$$P(need\ for\ RRT\ with\ HES)$$

$$= \frac{OR\ (need\ for\ RRT, crystalloid\ vs.\ HES) * \frac{P\ (need\ for\ RRT\ with\ crystalloid)}{1 - P(need\ for\ RRT\ with\ crystalloid)}}{1 + [OR\ (need\ for\ RRT, crystalloid\ vs.\ HES) * \frac{P\ (need\ for\ RRT\ with\ crystalloid)}{1 - P(need\ for\ RRT\ with\ crystalloid)}]}$$

Table 2. Formulae Used to Generate Cost and Effectiveness Estimates for the Various Payoffs in the Model.

Payoff	Calculation Formula
Costs	
Cost of treatment with crystalloid at survival (Path 1)	cSepsisGen
Cost of treatment with crystalloid at death (Path 2)	cSepsisGen
Cost of treatment with albumin at survival (Path 3)	cAlb + cSepsisGen
Cost of treatment with albumin at death (Path 4)	cAlb + cSepsisGen
Cost of treatment with hydroxyethyl starch – Survival/Renal dysfunction/Bleeding (Path 5)	cHES + cSepsisGen + cRenal + cBleeding
Cost of treatment with hydroxyethyl starch – Survival/Renal dysfunction/No bleeding (Path 6)	cHES+ cSepsisGen + cRenal
Cost of treatment with hydroxyethyl starch – Survival/No renal dysfunction/Bleeding (Path 7)	cHES + cSepsisGen + cBleeding
Cost of treatment with hydroxyethyl starch – Survival/No renal dysfunction/No bleeding (Path 8)	cHES + cSepsisGen
Cost of treatment with hydroxyethyl starch – death (Path 9)	cHES+ cSepsisGen
Effectiveness using DEALE [23]	
Effectiveness of treatment with crystalloid† (Path 1)	1/([1/LEgenpop]+(pDeadSep - [1/LEgenpop]))
Effectiveness of treatment with albumin† (Path 3)	1/([1/LEgenpop]+(pDeadAlb - [1/LEgenpop]))
Effectiveness of treatment with hydroxyethyl starch – Survival/Renal/Bleeding† (Path 5)	1/([1/LEgenpop]+[pDeadRenal-(pDeadHES90+pDeadHES)-[1/LEgenpop]]+[(pDeadHES90+pDeadHES)-pDeadBleed-[1/LEgenpop]]+[(pDeadHES90+pDeadHES)-[1/Legenpop]])
Effectiveness of treatment with hydroxyethyl starch – Survival/Renal/No Bleeding† (Path 6)	1/([1/LEgenpop]+[pDeadRenal-(pDeadHES90+pDeadHES)-[1/LEgenpop]]+[(pDeadHES90+pDeadHES)-[1/Legenpop]])
Effectiveness of treatment with hydroxyethyl starch – Survival/No Renal/Bleeding† (Path 7)	1/([1/LEgenpop]+[(pDeadHES90+pDeadHES)-pDeadBleed-[1/LEgenpop]]+[(pDeadHES90+pDeadHES)-[1/Legenpop]])
Effectiveness of treatment with hydroxyethyl starch – Survival/No Renal/No Bleeding† (Path 8)	1/([1/LEgenpop]+[(pDeadHES90+pDeadHES)-[1/Legenpop]])
Effectiveness of treatment with any fluid at death (Path 2, 4,9)	0

*Refer (Table **1**) for definitions of the abbreviations in the formula.

The relevant expressions used to generate estimates in life years (LY) gained or lost as effectiveness of the three fluids are shown in the formulae included in the model (Table **2**). The average age of patients in the HCUPnet severe sepsis cohort (ICD 9: 995.92) was 64 years. Hence the life expectancy of the general population at age 64 was used to estimate DEALE in the various disease paths. Depending on the path of complications with hydroxyethyl starch, the probability of mortality with RRT or bleeding in critically ill patients was used to calculate patient specific disease mortality (Table **2**). The effectiveness was assumed as zero at the time of death.

Sensitivity Analysis

We checked the robustness of the model with one-way and probabilistic sensitivity analyses (SA) by varying parameters of interest. We chose variables for which there was expected uncertainty or where alternate values were available in the same source (Table **1**). All the cost variables, the excess probability of renal replacement therapy with HES and probability of mortality after renal replacement therapy (RRT) were subjected to one-way SA. The ranges for cost of treatment and complications were obtained from the literature (Table **1**) and were inflated to 2012 costs where necessary.

Probabilistic sensitivity analysis was conducted on the cost variables – treatment of sepsis with standard of care, renal replacement therapy, treatment of bleeding; probabilities of mortality with standard of care, albumin and HES, probabilities of mortality in bleeding and after RRT and ex-

cess probability of renal replacement therapy with HES. An appropriate distribution was chosen depending on the characteristics described in the literature for these variables (Table **1**).

RESULTS

Increased effectiveness (life years gained) resulted from albumin treatment relative to both hydroxyethyl starch and crystalloid, and decreased cost relative to hydroxyethyl starch. Albumin treatment led to an increased life gain of 0.21 life years relative to standard treatment for sepsis. Treatment with hydroxyethyl starch led to a loss of 0.85 life years relative to standard treatment (Table **3**).

Total medical costs rose with albumin treatment by the estimated cost of albumin in comparison to crystalloid, and rose further when using hydroxyethyl starch because of the relevant costs with the associated morbidities. Treatment with albumin dominated (more effective at lower cost) treatment with hydroxyethyl starch. Although the total cost of crystalloid was lower compared to albumin, the cost per life year saved was the lowest for albumin (Table **3**). One-way sensitivity analysis showed that the outcome was independent of the cost of albumin over a wide range.

The one-way sensitivity analyses (Table **4**) indicated that the cost of RRT makes the most impact on the model with changes in cost per life year of hydroxyethyl starch. The cost of treatment fluids and blood for bleeding complications did not have a large impact in the model outcomes with a relatively minor influence on the cost per life year gained. The

Table 3. Cost Effectiveness Results – Base Case.

Fluid	Life Expectancy (LY)	Total medical Costs	Incremental Costs	Total Costs per LY
Crystalloid	2.00	$20,133	Reference	$10,036
Albumin	2.21	$20,403	$270	$9,253
Hydroxyethyl starch	1.15	$28,091	$76	$24,363

*LY – Life Years
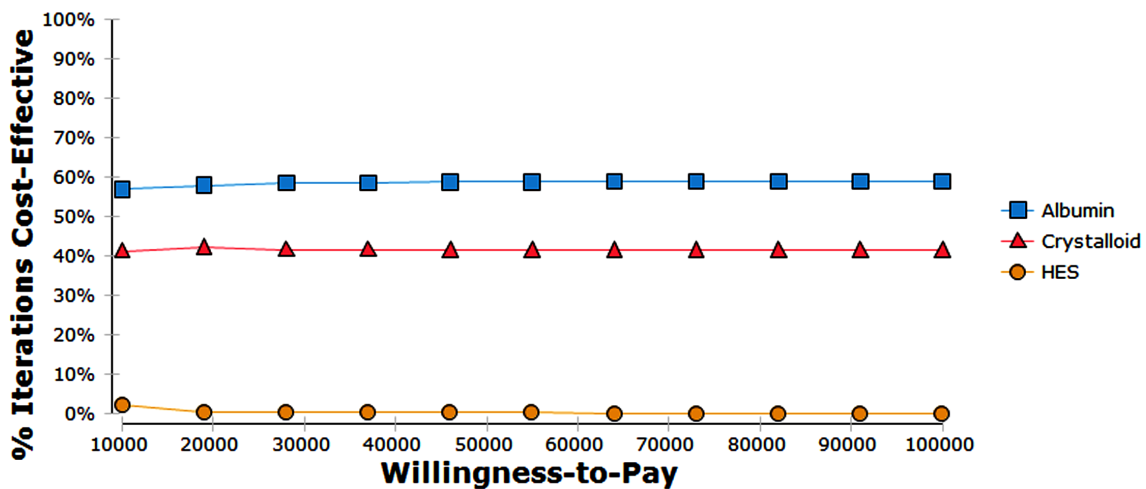
Fig. (2). Cost Effectiveness Acceptability Curve. The percentages of iterations which are cost effective relative to different willingness-to-pay (WTP) thresholds are shown for the alternate treatments. Albumin is the most cost effective across a wide range of WTP thresholds (in US$).

Table 4. Results of One-way Sensitivity Analysis.

Variable			Total Cost/LY (Low)	Total Cost/LY (High)
Cost of standard care of sepsis		Crystalloid	$8,029	$12,044
		Albumin	$7,426	$11,079
		Hydroxyethyl starch	$21,142	$27,585
Cost of albumin		Crystalloid	$10,036	$10,036
		Albumin	$9,243	$9,584
		Hydroxyethyl starch	$24,363	$24,363
Cost of HES		Crystalloid	$10,036	$10,036
		Albumin	$9,253	$9,253
		Hydroxyethyl starch	$24,320	$24,407
Cost of RRT		Crystalloid	$10,036	$10,036
		Albumin	$9,253	$9,253
		Hydroxyethyl starch	$20,656	$33,580
Cost of treatment of bleeding		Crystalloid	$10,036	$10,036
		Albumin	$9,253	$9,253
		Hydroxyethyl starch	$24,352	$24,374
Excess probability of renal replacement therapy with hydroxyethyl starch		Crystalloid	$10,036	$10,036
		Albumin	$9,253	$9,253
		Hydroxyethyl starch	$18,692	$30,093
Probability of mortality after RRT		Crystalloid	$10,036	$10,036
		Albumin	$9,253	$9,253
		Hydroxyethyl starch	$24,083	$24,599

cost of the current standard of care influenced all the treatment costs per life year but still showed the lowest cost per life year for albumin.

The cost-effectiveness acceptability curve (Fig. **2**) showed that, relative to the assigned threshold of US $10,000 per life year gained, albumin was cost-effective around 56% of the iterations followed by crystalloids with 40% of the iterations and HES with less than 5% of iterations.

DISCUSSION

In the current era of pressure on all health care budgets, hospital expenditures tend to be apportioned among devolved to semi-independent cost centers and are scrutinized in areas such as drug costs. Preference may be given to treatments that are relatively less expensive on an individual basis without assessing their effect on overall treatment outcome, risking an increase in total medical costs. In approaching a choice for fluid treatment for sepsis, a range of fluids present themselves. On a per unit basis, albumin is the costliest of these therapies, leading to hydroxyethyl starch being proposed as an alternative when colloid rather than crystalloid is the modality of choice.

Treatment choice has to take into account the possible adverse events of the fluids in question. In fluid therapies, such adverse events include renal and hemostatic dysfunction which have been associated with hydroxyethyl starches for many years, but not with albumin or crystalloid solutions. Claims that recently introduced modifications have led to low molecular weight variants which are not associated with renal dysfunction are not borne out by meta-analysis [15,16] and recent clinical trials [28,34]. Regulatory authorities charged with monitoring pharmacovigilance data have arrived at the conclusion that all HES products behave as a class relative to these adverse events and that their marketing authorization should be suspended [36]. Our study's assumption that such effects are limited to HES is based on recent meta-analyses comparing the safety of colloids, which have concluded that renal toxicity is colloid specific, with albumin displaying renal protection at all formulations[37], while being devoid of any specific effect on hemostasis [38].

The other key assumption of our model is that all hydroxyethyl starch, crystalloids and albumin preparations show biopharmaceutical equivalence within each product class. As discussed above, clinical trials do not support the contention that succeeding generations of hydroxyethyl starch demonstrate safety enhancements in relation to the key effects included in this study, leading to regulatory authorities considering them as a homogenous class therapeutically irrespective of any biochemical or pharmacoki-

netic differences. We make similar assumptions regarding albumin solutions, noting that the United States Food and Drug Administration (US-FDA) has reached this conclusion regarding albumin solutions [39]. Similarly, while some studies indicate that balanced crystalloid solutions may better maintain physiological profiles [40], this has not been confirmed in meta-analysis of therapeutic effects. Nevertheless, the findings of a recent single-center, sequential, observational study [41], indicating that chloride-rich fluids, including saline and albumin, were associated with increased renal injury and need for RRT in ICU patients is of interest and should inform future further trials allowing this issue to discriminate further between individual fluids than did this sequential study, which, because of its particular design, did not lend itself to incorporation into our NMA. Since the available evidence continues to indicate a lack of adverse renal effects from albumin [37], it is likely that the burden of renal injury observed by Yunos *et al.* was caused by other chloride-rich fluids, the use of which cannot be considered to be cost-effective if further studies confirm Yunos et al's results. Formulations of albumin in balanced salt solutions would be needed to address directly this issue, and it is unlikely that such products will be available, or needed, for trial in the foreseeable future.

A previous study [42] used the preliminary data extracted for the sepsis patient subset of the SAFE trial to demonstrate that albumin, at a cost of €617 per life year saved, is cost-effective relative to other ICU interventions. Since this study's publication, the SAFE study sepsis-subgroup has been further analyzed [8] and the survival benefit ensuing from albumin has been also been indicated through a meta-analysis [9] and more recent clinical trials [10,11]. Concurrently, trials [28], [34] and meta-analyses summarized in [43] have continued to assess the safety of HES solution. These recent data informed our meta-analysis generating a hypothetical comparison of albumin and hydroxyethyl starch fluid therapy in sepsis, using as our patient population of the sepsis patient cohort in the US as derived from ICD 9 code: 995.92 category [22]. This analysis was used to derive survival probabilities in order to allow a cost-effectiveness comparison using decision analysis.

The results of our decision analysis indicate that albumin dominates hydroxyethyl starch and is cost effective relative to crystalloid. The analysis yielded a gain of 0.21 life years in albumin relative to crystalloid and 0.85 life years relative to HES. The total cost per life year with albumin is also the lowest at $9,253. Sensitivity analysis indicates that this result is robust over a range of albumin, prices. We incorporated in our base case analysis the overall medical costs of treating severe sepsis as extracted from the HCUPnet database [22]. Compared to the substantial total medical cost of current practice in treating sepsis, the cost of fluid therapy is modest and has little effect on cost-effectiveness.

Our NMA informing this cost-effectiveness model's life expectancy inputs [18] was constructed and published before the publication of the recent CRISTAL trial [19] and we reworked the NMA to include the CRISTAL data. The CRISTAL study indicated that colloids of various types were superior to crystalloids in improving 90 day, but not 28 day mortality, Since this is the only study including 90 day mor-

tality for albumin, we were not able to include this result in our NMA, but have calculated that the odds ratio for 90 day mortality comparing HES and albumin in the CRISTAL study is 1.0, indicating equivalence between HES and albumin. Incorporating the 28 day mortality data from CRISTAL in the NMA did not affect the ranking of fluid therapies we reported previously and did not affect the cost-effectiveness of the different fluid treatments which we found in the present study. Given that less than 6% of the patients in CRISTAL were given albumin, its contribution to the overall result is questionable, but CRISTAL is the only recent study not reporting increased renal problems and/or increased mortality with HES, and the authors have speculated on the differences from the outcomes of recent clinical trials which have led to severe restrictions being put on these products, Differences in HES dosage and possible renal injury from the preponderance of chloride-rich crystalloids used in the trial may contribute to the differences observed.

The incidence and expense of sepsis are extremely high as is the mortality rate post-discharge among sepsis patients is high [44], and the relatively modest - 0.21 life years gained - increase in life expectancy predicted by the model represents a 11% increase relative to standard practice. The post-hospital mortality of sepsis patients depends on age [45] and applying the model developed in the current study may allow further cost-effectiveness assessment of the use of albumin in subsets of patients. Furthermore, extending the current analysis to a longer term and assessing the effect on quality of life estimates may inform the cost of one quality adjusted life year (QALY) of sepsis treatment. Such studies are planned for the future.

This study suffers from certain limitations. The lack of enough data from trials directly comparing albumin with hydroxyethyl starch necessitated the extraction of hypothetical variables from meta-analyses in order to populate the model and estimate payoffs. We acknowledge that the key assumption that the three modalities studied are biopharmaceutically equivalent within a class is contentious, but we note that this assumption underpins all the systematic reviews pertaining to these products. This issue is most contentious in relation to hydroxyethyl starch, where the relative safety of recent formulations has been emphasized [14], but we note the conclusions of a recent NIH/FDA workshop that over a longer period of time hydroxyethyl starch has been associated with serious adverse events in sepsis irrespective of the formulation used [35], conclusions which underpin the recent regulatory decisions worldwide to restrict access to these products [36,43]. Finally, we recognize the limitations imposed by the paucity of head to head trials between albumin and HES, necessitating the hypothetical comparison proposed in the model. These issues all form part of the considerations which regulatory agencies, amongst the range of stakeholders charged with pharmacovigilance, must consider when approaching decisions regarding a class of drugs. As a result of the data accrued regarding the relative safety of fluids assessed in this study, both the European Medicines Agency [36] and the United States Food and Drug Administration (FDA) [43] have placed substantial restrictions on the use of HES solutions as a class. While warnings such as those imposed by the FDA do not result in the removal of the products from the clinical environment, they confirm the

concerns raised by the use of these drugs in the present study. Furthermore, on the basis of our work, we propose that caution is justified when funding therapeutic interventions on the basis of simple comparisons of the cost of products as the sole criteria. In estimating the total costs of health care, models such as we propose are useful tools to assist decision making.

CONCLUSION

Using data generated from large recent clinical trials of fluid therapies in acute care, a cost-effective analysis comparing treatments was developed. The use of albumin in septic patients, when colloid fluid therapy is indicated, shows superior cost-effectiveness to hydroxyethyl starch. Hence, crude assessments of the basic per unit costs by hospital pharmacies are inadequate and inappropriate tools for decision making. An appreciation of these principles should lead to better and more cost-effective care for patients with sepsis. This study emphasizes the use of clinical data in informing health policy and decision making in the current era of budgetary pressures.

CONFLICT OF INTEREST

Albert Farrugia, Sonia Balboni, Megha Bansal and Mary Clare Kimber provide services to the plasma protein therapeutics industry, which includes the manufacturers of therapies described in this work.

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