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An International Survey of Emergency and Critical Care Medicine Physicians' Fluid Resuscitation Practices for Adult Patients with Early Septic Shock

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An International Survey of Emergency and Critical Care Medicine Physicians' Fluid Resuscitation Practices for Adult Patients with Early Septic Shock

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ABSTRACT:

Objectives:

Evidence to guide fluid resuscitation evidence in sepsis continues to evolve. We conducted an international survey of emergency and critical care physicians to describe current stated practice and practice variation related to the quantity, rapidity and type of resuscitation fluid administered in early septic shock to inform the design of future septic shock fluid resuscitation trials.

Methods:

Using a web-based survey tool, we invited critical care and emergency physicians in Canada, the United Kingdom, Scandinavia, and Saudi Arabia to complete a self-administered electronic survey.

Results:

A total of 1097 physicians' responses were included. One litre was the most frequent quantity of resuscitation fluid physicians indicated they would administer at a time (46.9%, n=499). Most (63.0%, n=671) stated that they would administer the fluid challenges as quickly as possible. Overall, normal saline and Ringer's solutions were the preferred crystalloid fluids used 'often' or 'always' in 53.1% (n=556) and 60.5% (n=632) of instances, respectively. However, emergency physicians indicated they would use normal saline 'often' or 'always' in 83.9% (n=376) of instances while critical care physicians said they would use saline 'often' or 'always' in 27.9% (n=150) of instances. Only 1.0% (n=10) of respondents indicated they would use hydroxyethyl starch 'often' or 'always'; use of 5% (5.6% (n=59)) or 20-25% albumin (1.3% (n=14)) was also infrequent. The majority (88.4%, n=896) of respondents indicated that a large randomized controlled trial comparing 5% albumin to a crystalloid fluid in early septic shock was important to conduct.

Conclusions:

International critical care and emergency physicians stated that they rapidly infuse large volumes of crystalloid resuscitation fluid in early septic shock. Colloid use, specifically the use of

albumin, was infrequently reported. Our survey identifies the need to conduct a trial on the efficacy of albumin and crystalloids on 90-day mortality in patients with early septic shock.

Study Strengths and Limitations:

- This survey included a very large sample which was international in scope.
- The survey was designed to be short, simple, and specific to the early resuscitative phase of septic shock so that it would take at most 5 minutes to complete.
- Since the survey focused on the early resuscitative phase of septic shock, the responses to questions may not be generalizable to later phases of septic shock or specific sub populations of patients with septic shock.
- Due to the variable methods used for survey distribution, we could not summarize an accurate response proportion.

BACKGROUND:

Fluid resuscitation is a vital, first line intervention for all patients with septic shock. Management guidelines recommend rapid boluses of resuscitation fluid over the first few hours with the goal of regaining hemodynamic stability, optimizing organ perfusion and ultimately, improving outcomes and preventing death[1]. While fluid resuscitation is a life-saving intervention, until recently, high quality evidence to guide fluid choice and resuscitation practices has been lacking.

A multi-centre fluid resuscitation trial of children with severe fever and hypoperfusion from East Africa questioned how aggressively we should administer resuscitation fluids in sepsis[2]. This trial found that fluid boluses, as compared to the administration of intravenous maintenance fluids, increased the risk of death at 48 hours and challenges current resuscitation guidelines[1]. Evidence from randomized trials studying the use of colloids has also recently emerged. In 2004, our group conducted a survey of early septic shock resuscitation practices in Canadian critical care physicians and found that hydroxyethyl starch (HES) fluid was used commonly, reportedly 51% of the time[3]. Since the time of this survey, however, data from randomized trials and systematic reviews have demonstrated clear harms caused by HES in critically ill patients, particularly those with sepsis[4-8]. Although a recent systematic review of albumin in sepsis found no overall mortality benefit[9], two sub group analyses from recent randomized trials comparing albumin to crystalloid fluid in the critically ill and severe sepsis and septic shock found reductions in mortality at 28 and 90 days respectively [10,11].

In the context of evolving literature to guide practice, we conducted an early septic shock fluid resuscitation survey to inform the design and provide justification for future early septic shock fluid resuscitation trials comparing 5% albumin versus crystalloid fluid on 90-day mortality. Our survey had two objectives: 1) to describe practice variation among emergency and critical care physicians regarding the quantity, rapidity and type of fluid administered during early septic shock resuscitation and 2) to elicit views of a future early septic shock fluid resuscitation trial comparing 5% albumin versus crystalloid fluid on 90-day mortality by eliciting from respondents

the minimal clinically important difference between fluid intervention and control arms that would inform their practice, as well understanding the perceived importance of and respondents' willingness to enroll into such a future trial.

MATERIALS AND METHODS:

Identification of Study Participants and Survey Distribution:

Our target population consisted of critical care and emergency physicians in Canada, the United Kingdom, Scandinavia, and Saudi Arabia who provide care for adults patients (≥ 18 years of age) with septic shock. These countries were selected because research and opinion leaders in these counties had expressed interest in collaborating on an international trial on early fluid resuscitation.

Participants were contacted by their respective critical care or emergency medicine professional societies and through direct contact with lead site investigators using a standardized email containing a web link to the survey. Respondents activated the web link and completed the survey instrument online. The survey was distributed in January and February 2014. To maximize responses, non-respondents received up to two email reminders.

Survey Development:

We generated items for the survey instrument through literature review and consultation with international investigators representing emergency and critical care medicine. Items were reduced and formatted to reduce respondent burden and maximize the response rate. The survey was pilot tested by our investigative team and critical care research fellows at the University of Ottawa in Ottawa, Canada for clinical sensibility and with a target time to completion of 5 minutes. The survey was structured using a web based survey platform (FluidSurveys). Research ethics board approval was sought as required by lead investigators for each country that participated in the survey.

Survey Content:

The survey presented a typical patient with early septic shock in the emergency department(ED); see survey, Supplementary Appendix I. This patient was introduced as a 55-year old 70 Kg female who had just arrived in the ED with suspected septic shock. She was confused, with a blood pressure of 70/30, heart rate 135 beats per minute, respiratory rate of 25 breaths per minute, temperature 39.5 degrees Celsius and oxygen saturation of 96% on 3 litres by nasal prongs. She had already received a total of 1 liter of normal saline over 15 minutes in the ED.

Respondents were then asked a series of questions: the first was to document the quantity and rapidity of fluid administration, and the second question examined the type of resuscitation fluids that they would use in both a "typical" and an "ideal" situation to resuscitate the patient described above. An "ideal" situation was proposed for respondents to ascertain the fluid type given that a physician may wish to give a fluid but that fluid may not be readily available to them in practice (e.g., fluid not stocked or immediately available in the department). For each of these questions, respondents answered based on a 5 point Likert scale (i.e., never, rarely, sometimes, often, always).

To inform the design of an early septic shock fluid resuscitation trial comparing 5% albumin to a crystalloid fluid on the primary outcome of 90-day mortality, we asked respondents to provide their views on an estimate of the minimal clinically important difference between the fluid intervention and control arms that would be required to inform their practice (response options: 1%, 2.5%, 5%, 7.5%, and 10%). Two further questions were posed to determine the perceived importance of (response options: not at all important, not very important, somewhat important, important, very important) and their willingness to enroll patients into such a trial (response options: yes, no).

We also documented respondents' primary specialty and their practice experience in emergency medicine and/or critical care.

Survey Data Collection and Analysis:

All data were collected electronically through FluidSurveys (Ottawa, ON) and were housed and managed on FluidSurveys'secure servers. Prior to analysis, raw data was exported to Microsoft Excel (Version 2010, Redmond, WA) for cleaning and then exported to SAS (Version 9.2, by SAS Institute Inc., Cary, NC) for analysis.

All data are presented with numbers and proportions for dichotomous and categorical variables, and with means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, as appropriate. The 5 point Likert scale responses were combined into 'often or always', 'sometimes', and 'rarely or never' for purposes of data presentation. The data for all respondents were also described according to whether respondents were critical care or emergency medicine physicians. Post - hoc, we calculated absolute differences in proportions and 95 percent confidence intervals (CI) between typical and ideal fluid use for all respondents and by primary specialty (critical care physicians and emergency physicians) respectively. Differences in proportions with 95% CIs for emergency and critical care physicians for typical and ideal fluid were also calculated.

RESULTS:

Study Sample:

A total of 1139 physicians responded to the survey; 16 respondents were not emergency or critical care physicians, a further 15 did not provide care for adult patients with septic shock, and 11 physicians did not respond to one (n=10) or both (n=1) of these questions. Thus, a total of 1097 physicians' responses were included in the final results. Of these, 64% (n = 702) were from the United Kingdom, 26% (n = 290) were from Canada, and the remaining 10% (n = 105) were from Saudi Arabi (6.6%, n=72) and Scandinavia (3.0%, n=33).

Demographics and Training:

A total of 90% (n=985) of physicians responded to the primary specialty question. Of these responses, 45.5% (n = 448) of physicians indicated that their primary specialty was emergency medicine. The average number of years spent in clinical practice was 10 (SD: 8).

Quantity and Rapidity of Administration of Resuscitation Fluids:

Physicians most commonly indicated they would administer one litre of fluid for early septic shock (46.9%, n=499), followed by 500 mls (32.0%, n=340) (see Table 1). When examined by primary specialty, one litre (62.3%, n=279) and 500 mls (41.5%, n=223) were the most frequent responses for emergency and critical care physicians, respectively. Most physicians (63%, n=671) stated that they would administer the fluid challenges as quickly as possible; this response remained the most frequent when the data were examined by emergency and critical care physicians (73.2%, n=328 and 56.4%, n=303, respectively).

Table 1: Quantity and Rapidity of Fluid Resuscitation by All Respondents, Critical Care and Emergency Physicians

Quantity n (%)		Rapidity n (%)	
All Respondents			
(n=1064)		**(n=1065)**	
100 mls	2 (0.2)	5 mins	66 (6.2)
250 mls	123 (11.6)	10 mins	98 (9.2)
500 mls	340 (32.0)	15 mins	131 (12.3)
750 mls	9 (0.8)	30 mins	81 (7.6)
1000 mls	499 (46.9)	1 hour	18 (1.7)
Other	91 (8.6)	As quickly as possible	671 (63.0)
Critical Care Physicians			
(n=537)		**(n=537)**	
100 mls	2 (0.4)	5 mins	45 (8.4)
250 mls	86 (16.0)	10 mins	64 (11.9)
500 mls	223 (41.5)	15 mins	75 (14.0)
750 mls	6 (1.1)	30 mins	42 (7.8)
1000 mls	194 (36.1)	1 hour	8 (1.5)
Other	26 (4.8)	As quickly as possible	303 (56.4)
Emergency Physicians			
(n=448)		**(n=448)**	
100 mls	0 (0)	5 mins	12 (2.7)
250 mls	21 (4.7)	10 mins	25 (5.6)
500 mls	90 (20.1)	15 mins	43 (9.6)
750 mls	3 (0.7)	30 mins	35 (7.8)
1000 mls	279 (62.3)	1 hour	5 (1.1)
Other	55 (12.3)	As quickly as possible	328 (73.2)

Type of Resuscitation Fluid Typically and Ideally Administered:

Normal saline and Ringer's solutions were used typically 'often' or ' always' for early septic shock resuscitation 53.1% (n=556) and 60.5% (n=632) of the time, respectively (see Figure 1 and Table 2). In contrast, respondents infrequently used Plasma-Lyte (10.1%, n=106), 5% albumin (5.6%, n=59), 20-25% albumin (1.3%, n=14), and gelatins (7.0%, n=73) 'often' or 'always' in early resuscitative efforts. Only 1.0% (n=10) of respondents indicated they would use hydroxyethyl starch 'often' or 'always' in the resuscitative phase of septic shock.

When asked about the use of these fluids in the ideal setting where they would be immediately available, use of Plasma-Lyte and 5% albumin 'often' or 'always' increased the most (Plasma-Lyte from 10.1% (n=106) to 25.3% (n=264) (absolute difference (AD)= -15.2%;95% CI:-17.5% to -12.9%) and 5% albumin from 5.6% (n=59) to 12.4% (n=129) (AD= -6.7%; 95% CI:-8.3% to -5.0%) (see Figure 2 and Supplementary Table 1).

When the typical use of crystalloid fluids was examined by primary specialty, emergency physicians indicated they would use normal saline 'often' or 'always' 83.9% (n=376) in contrast to critical care physicians who said they would use saline 27.9% (n=150) (AD = 56.0%;95% CI: 50.9% to 61.1%) (see Figure 1 and Supplementary Table 1). In the ideal setting, where these fluids would be immediately available, the two fluid type responses that increased the most for emergency physicians were Ringer's solutions from 35.3% (n=158) to 45.1% (n=202) (AD = -9.8; 95% CI: -13.3 to -6.4) and Plasma-Lyte from 2.9% (n=13) to 11.4% (n=51) (AD = -8.5; 95% CI: -11.2 to -5.8)) (see Figure 2, Supplementary Table 1). The two fluid type responses that increased the most in the ideal setting for critical care physicians were Plasma-Lyte (from 15.3% (n=82) to 36.5% (n=196), AD = -21.2; 95% CI: -24.9 to -17.6)) and 5% albumin (from 10.6% (n=57) to 20.5% (n=110), AD = -9.9; 95% CI: -12.6 to -7.1)).

A summary of typical and ideal fluid use by country is provided in Supplementary Table 2 and Supplementary Figures 1 and 2 respectively.

Table 2: Type of Resuscitation Fluid Typically & Ideally Administered by All Respondents, Critical Care and Emergency Physicians

	Typically Administered				Ideally Administered			
Type	Number Respondents	Never/Rarely n (%)	Sometimes n (%)	Often/Always n (%)	Number Respondents	Never/Rarely n (%)	Sometimes n (%)	Often/Always n (%)
All Respondents								
Normal Saline	(n=1047)	300 (28.7)	191 (18.2)	556 (53.1)	(n=1045)	384 (36.7)	165 (15.8)	496 (47.5)
Ringer's Solutions	(n=1045)	261 (25.0)	152 (14.5)	632 (60.5)	(n=1044)	232 (22.2)	141 (13.5)	671 (64.3)
Plasma-Lyte	(n=1045)	894 (85.6)	45 (4.3)	106 (10.1)	(n=1043)	716 (68.7)	63 (6.0)	264 (25.3)
5% Albumin	(n=1045)	873 (83.5)	113 (10.8)	59 (5.6)	(n=1044)	740 (70.9)	175 (16.8)	129 (12.4)
20% or 25% Albumin	(n=1044)	960 (92.0)	70 (6.7)	14 (1.3)	(n=1043)	911 (87.3)	101 (9.7)	31 (3.0)
Hydroxyethyl Starch	(n=1044)	1023 (98.0)	11 (1.1)	10 (1.0)	(n=1044)	1017 (97.4)	15 (1.4)	12 (1.1)
Gelatin	(n=1045)	868 (83.1)	104 (10.0)	73 (7.0)	(n=1044)	903 (86.5)	82 (7.9)	59 (5.7)
Critical Care Physicians								
Normal Saline	(n=537)	249 (46.4)	138 (25.7)	150 (27.9)	(n=537)	300 (55.9)	114 (21.2)	123 (22.9)
Ringer's Solutions	(n=537)	35 (6.5)	65 (12.1)	437 (81.4)	(n=537)	51 (9.5)	56 (10.4)	430 (80.1)
Plasma-Lyte	(n=537)	426 (79.3)	29 (5.4)	82 (15.3)	(n=537)	297 (55.3)	44 (8.2)	196 (36.5)
5% Albumin	(n=537)	383 (71.3)	97 (18.1)	57 (10.6)	(n=537)	310 (57.7)	117 (21.8)	110 (20.5)
20% or 25% Albumin	(n=537)	466(86.8)	58 (10.8)	13 (2.4)	(n=537)	442 (82.3)	71 (13.2)	24 (4.5)
Hydroxyethyl Starch	(n=537)	522 (97.2)	7 (1.3)	8 (1.5)	(n=537)	521 (97.0)	7 (1.3)	9 (1.7)
Gelatin	(n=537)	394 (73.4)	77 (14.3)	66 (12.3)	(n=537)	426 (79.3)	58 (10.8)	53 (9.9)
Emergency Physicians								
Normal Saline	(n=448)	28 (6.3)	44 (9.8)	376 (83.9)	(n=448)	61 (13.6)	41 (9.2)	346 (77.2)
Ringer's Solutions	(n=448)	211 (47.1)	79 (17.6)	158 (35.3)	(n=448)	170 (37.9)	76 (17.0)	202 (45.1)
Plasma -Lyte	(n=448)	422 (94.2)	13 (2.9)	13 (2.9)	(n=448)	381 (85.0)	16 (3.6)	51 (11.4)
5% Albumin	(n=448)	434 (96.9)	13 (2.9)	1 (0.2)	(n=448)	384 (85.7)	47 (10.5)	17 (3.8)
20% or 25% Albumin	(n=448)	441 (98.4)	7 (1.6)	0 (0)	(n=448)	423 (94.4)	20 (4.5)	5 (1.1)
Hydroxyethyl Starch	(n=448)	444 (99.1)	3 (0.7)	1 (0.2)	(n=448)	437 (97.5)	8 (1.8)	3 (0.7)
Gelatin	(n=448)	425 (94.9)	21 (4.7)	2 (0.4)	(n=448)	424 (94.6)	21 (4.7)	3 (0.7)

Views on a Future Early Septic Shock Fluid ResuscitationTrial

Most respondents indicated that the minimal clinically important difference (MCID) for a future trial comparing 5% albumin and a crystalloid fluid on 90-day mortality for early septic shock that would be required to maintain or change their practise was 5% (53.6%, 539/1005). MCIDs of 10% (16.3%, 164/1005), 7.5% (7.5%, 75/1005), 2.5% (19.1%, 192/1005), and 1% (3.5%, 35/1005) were less frequent responses. Respondents also indicated that a large randomized controlled trial comparing 5% albumin to a crystalloid fluid with a primary outcome of 90-day mortality was important to conduct as 88.4% (896/1014) of respondents indicated the trial was somewhat important (24.0%,243/1014), important (39.4%, 400/1014), or very important (25%,253/1014). Furthermore, 84.4% (851/1008) of respondents indicated that they would be willing to enroll patients into such a future clinical trial.

DISCUSSION:

Results of our large, international survey suggest that emergency and critical care physicians who assess and manage adult patients in the early resuscitative phase of septic shock prefer that fluid challenges (at least 500 mls) be administered as quickly as possible. When examined by primary specialty, critical care physicians indicated a preference to use Ringer's solutions compared to emergency physicians who indicated a preference to use normal saline. Although the reported use of Plasma-Lyte was infrequent, our survey data suggest that both emergency and critical care physicians would use more of this crystalloid fluid if it was readily available to them. Use of hydroxyethyl starch fluid was uncommon and the reported use of albumin (5% or 20-25%) was infrequent, although critical care physicians also indicated that they would use albumin more frequently if it was immediately available to them.

An abundance of observational evidence from large propensity-matched cohort studies in the surgical[12,13] and critically ill[14] populations,and a prospective sequential period study[15] in the critically ill suggest that high chloride fluids (e.g., normal saline) may be associated with excess mortality compared to lower chloride fluids such as Ringer's solutions or Plasma-Lyte. In addition, normal saline resuscitation has been associated with the subsequent use of renal

replacement therapy, increased post-operative infections, and prolonged hospital length of stay in hospital[12-15]. Despite these data, our survey, and a similar survey conducted in Scotland[16] suggests that emergency physicians prefer using normal saline while critical care physicians prefer Ringer's solutions in septic shock. The variability in stated practice between emergency and critical care physicians that was evident in our survey may in part reflect an absence of high quality evidence to support the preference of either of these fluids, although a recent network meta-analysis of randomized controlled fluid trials in sepsis found balanced crystalloids such as Ringer's or Plasma-Lyte as compared to normal saline were associated with a reduced odds of death[17]. However, since the reported use of both Ringer's solutions and Plasma-Lyte further increased when presented with an 'ideal', but still theoretical scenario in our survey, lack of availability of these fluids, or unit specific policies or protocols[18], may contribute to the reported practice variability we identified.

Very few emergency and critical care physicians indicated that they would use HES boluses in the early resuscitative phase septic shock. Thiscontrasts sharply to a septic shock resuscitation survey from 2004 in which Canadian critical care physicians reported that they would use HES fluids for early septic shock resuscitation 51% of the time. In the European intensive care unit fluid challenge observational study conducted in 2013, hydroxyethyl starch use accounted for only 10.8% of all fluid challenges in the study[18]. This apparent change in practice is likely related to high quality evidence from randomized controlled trials and systematic reviews in the last decade that now confirm starch fluids increase the risk of death and the use of renal replacement therapy in patients with severe sepsis and septic shock[5,6,8].

According to our survey results, the use of albumin in the early septic shock setting also remains infrequent despite the SAFE (A Comparison of Albumin to Saline for Fluid Resuscitation in the Intensive Care Unit) severe sepsis subgroup analysis that suggested 4% albumin compared to normal saline was associated with a significant reduction in 28-day mortality. After the conduct of this survey in 2014, the ALBIOS trial (Albumin Replacement for Patients with Severe Sepsis and Septic Shock) which compared 20% albumin with crystalloids versus crystalloids alone for patients with severe sepsis and septic shock was published. The ALBIOS

trial found a mortality benefit at 90 days for 20% albumin in a post hoc analysis of patients with septic shock but not those with severe sepsis[11]. If practice was influenced by that trial, it is possible that the albumin responses in our survey under-represent current use in early septic shock.

There are several weaknesses of this survey. First, a denominator could not be calculated to ascertain a response proportion because of the variable methods we used to distribute the survey. Second, only resuscitation questions were asked in relation to one hypothetical early septic shock scenario and as such, it is not possible to comment on fluid resuscitation practices for patients in the later phase of septic shock or with specific physiological characteristics (e.g., hypoalbuminemia or acute respiratory distress syndrome). This survey was, however, international in scope and large (~1000 responses), of which nearly 50% were emergency physicians. Although answers to questions related to other aspects of septic shock management were not obtained, the answers provide robust information regarding the fluid resuscitation practices of a wide variety of physicians managing patients in the early resuscitative phase septic shock. Furthermore, the survey was designed to be brief and take less than 5 minutes to complete to maximize responses to each question. That goal was achieved, since at least 95% of respondents answered each of the resuscitation questions.

In summary, in the resuscitative phase of septic shock, physician practice as stated in this international survey is to administer large volumes of resuscitation fluid over a short period of time. Although normal saline and Ringer's solutions are the two most common crystalloid fluids, stated preferences differ between emergency and critical care physicians. Most physicians support a future trial of albumin compared with crystalloid fluid in the early phase of septic shock.

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COMPETING INTERESTS:

FluidSurveys involvement in the project was limited to providing the secure platform that allowed the research team to collect data. AP has received grant support from CSL Behring and Fresenius Kabi and LM has received grant support from CSL Behring, all of which is outside of this submitted work. SMB has consulted for Baxter Healthcare Corp.

DATA SHARING STATEMENT:

There are no additional data to share.

CONTRIBUTORSHIP:

LM, DF, BHR, TW, AG, AP, YA, and JM conceived the survey design. LM drafted the manuscript and all authors contributed to interpretation of the data and critical revisions of the manuscript. All authors have given permission to submit this manuscript for publication.

FIGURE LEGENDS:

Figure 1: ALL = All respondents, CCP = Critical Care Physicians, EP = Emergency Physicians

Figure 2: ALL = All respondents, CCP = Critical Care Physicians, EP = Emergency Physicians

Supplementary Figure 1: CAN = Canada, UK = United Kingdom, SCAN = Scandinavia, SA = Saudi Arabia

Supplementary Figure 2: CAN = Canada, UK = United Kingdom, SCAN = Scandinavia, SA = Saudi Arabia

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Appendix 1: Early Septic Shock Fluid Resuscitation Survey

This survey is directed to critical care and emergency medicine physicians who primarily care for adult patients.This survey will take less than 5 minutes to complete. All results will be reported in aggregate numbers without personal or institutional identifying information. The Research Ethics Board of the The Ottawa Hospital-Ottawa Hospital Research Institute has approved this study.

Do you practice critical care medicine or emergency medicine?

- ○ Yes
- ○ No

Do you treat adult patients in the intensive care unit or the emergency department?

- ○ Yes
- ○ No

Consider the following scenario: You have been asked to see a 55 year old, 70 Kg female who has just arrived in the emergency department (ED) with suspected septic shock. She is confused, with a blood pressure of 70/30, heart rate 135 beats per minute, respiratory rate of 25 breaths per minute, temperature 39.5 degrees Celsius and oxygen saturation of 96% on 3 liters by nasal prongs. She has already received a total of 1 liter of normal saline over 15 minutes in the emergency department.

(1a) For this patient, how much resuscitation fluid would you typically administer at a time?

- ○ 100 mls
- ○ 250 mls
- ○ 500 mls
- ○ 750 mls
- ○ 1000 mls
- ○ Other quantity, please specify... _____

(1b) For this patient, how fast would you typically administer administer this fluid challenge(s)?

- ○ 5 mins
- ○ 10 mins
- ○ 15 mins
- ○ 30 mins
- ○ 1 hour
- ○ As quickly as possible

(2a) What type(s) of resuscitation fluid do you typically administer during the course of early resuscitation from septic shock?

Please provide an answer for each option

	Never	Rarely	Sometimes	Often	Always
Normal Saline	○	○	○	○	○
Ringers Lactate/Acetate or Hartmanns	○	○	○	○	○
Plasmalyte	○	○	○	○	○
5% Albumin	○	○	○	○	○
20% or 25% Albumin	○	○	○	○	○
Hydroxyethyl Starch	○	○	○	○	○
Gelatin	○	○	○	○	○

(2b) What type(s) of resuscitation fluid would you ideally administer during the course of early resuscitation from septic shock? Imagine that all the fluids are immediately available.

Please provide an answer for each option

	Never	Rarely	Sometimes	Often	Always
Normal Saline	○	○	○	○	○
Ringers Lactate/Acetate or Hartmanns.	○	○	○	○	○
Plasmalyte	○	○	○	○	○
5% Albumin	○	○	○	○	○
20% or 25% Albumin	○	○	○	○	○
Hydroxyethyl Starch	○	○	○	○	○
Gelatin	○	○	○	○	○

The following series of questions pertain to an early septic shock fluid resuscitation randomized controlled trial that we are planning. The trial will ask the following question: Does 5% albumin, compared to a crystalloid fluid reduce 90 day mortality due to septic shock?

(3) What would you consider the minimal clinically important difference (absolute risk difference) between our colloid arm (5% albumin) and crystalloid arm(s) that would change or maintain your practise? To answer this question, assume that 5% albumin is the superior fluid and the baseline risk of death at 90 days is 35%.

- ○ 1%
- ○ 2.5%
- ○ 5%
- ○ 7.5%
- ○ 10%

(4) Would you be willing to enrol patients in a pragmatic international early septic shock fluid resuscitation trial to compare the effectiveness of 5% albumin versus a crystalloid fluid(s) on 90 day mortality?

- ○ Yes
- ○ No

(5) How important is such a trial?

- ○ Very important
- ○ Important
- ○ Somewhat important
- ○ Not very important
- ○ Not at all important

How many years have you been in Intensive Care or Emergency Medicine practice since completing your training?

Please indicate your primary speciality.

- ○ Internal Medicine
- ○ Surgery
- ○ Anesthesia
- ○ Emergency Medicine
- ○ Critical Care
- ○ Other, please specify _____

Figure 1: Type of Resuscitation Fluid Typically Administered by All Respondents, Critical Care and Emergency Physicians

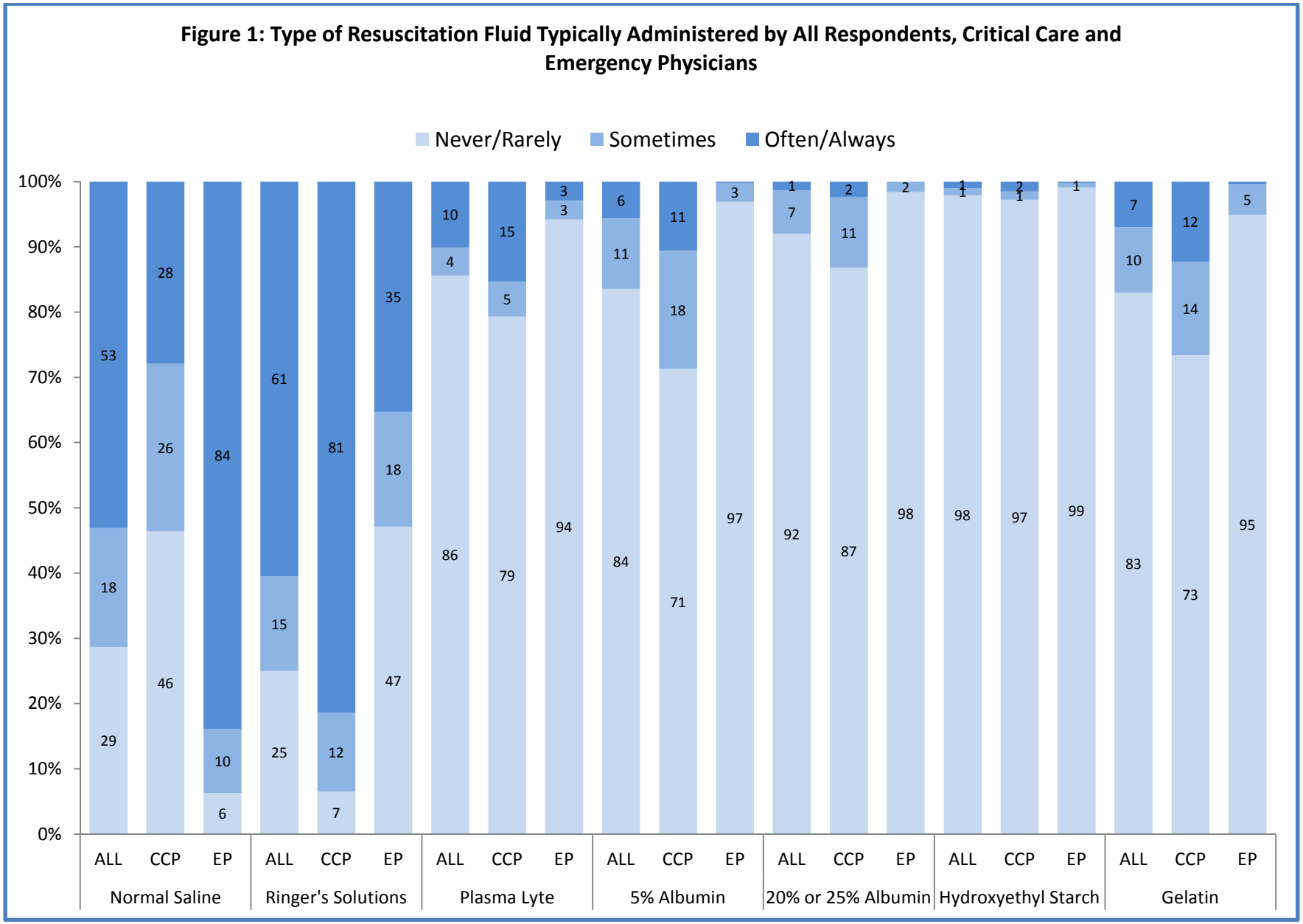
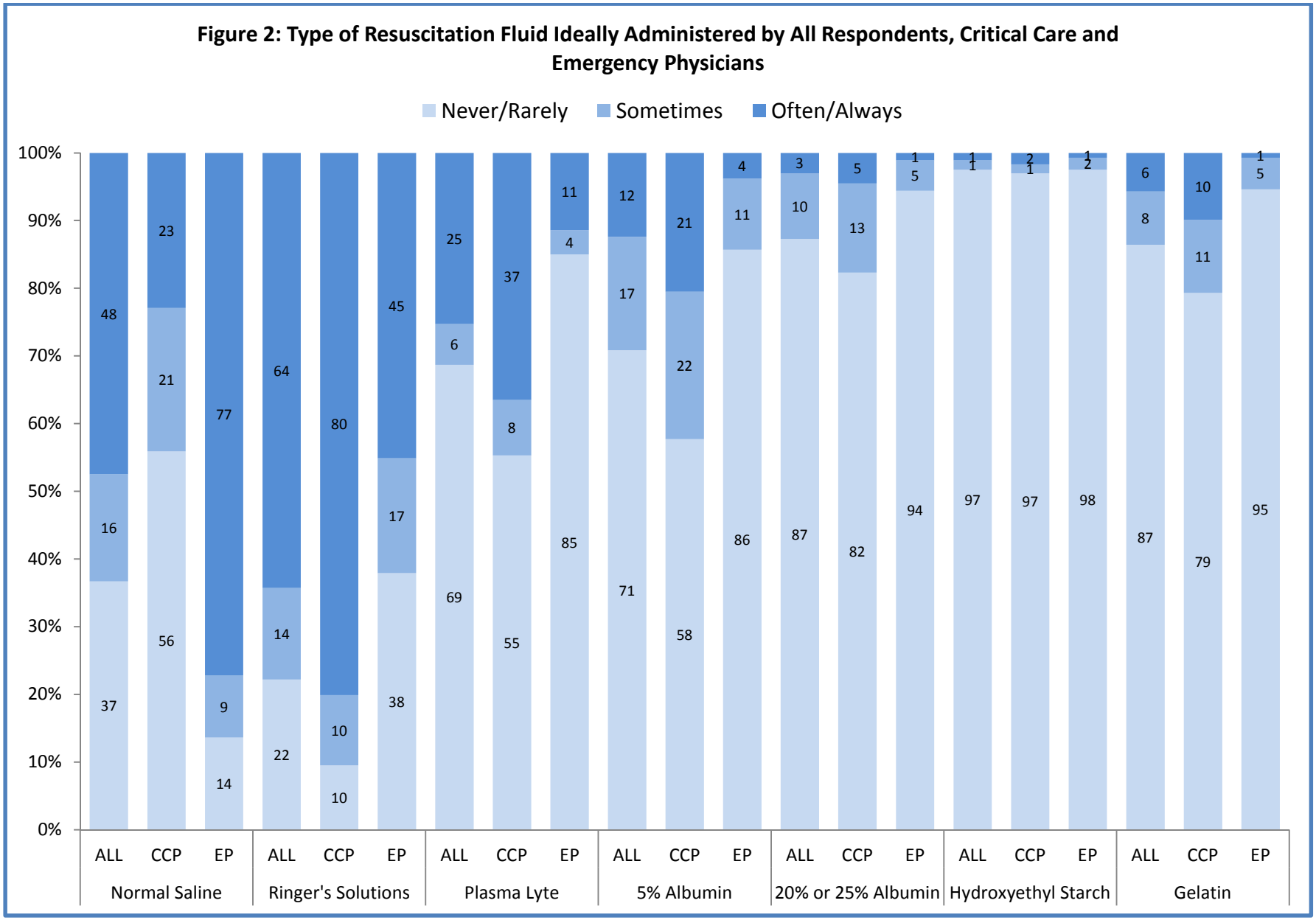
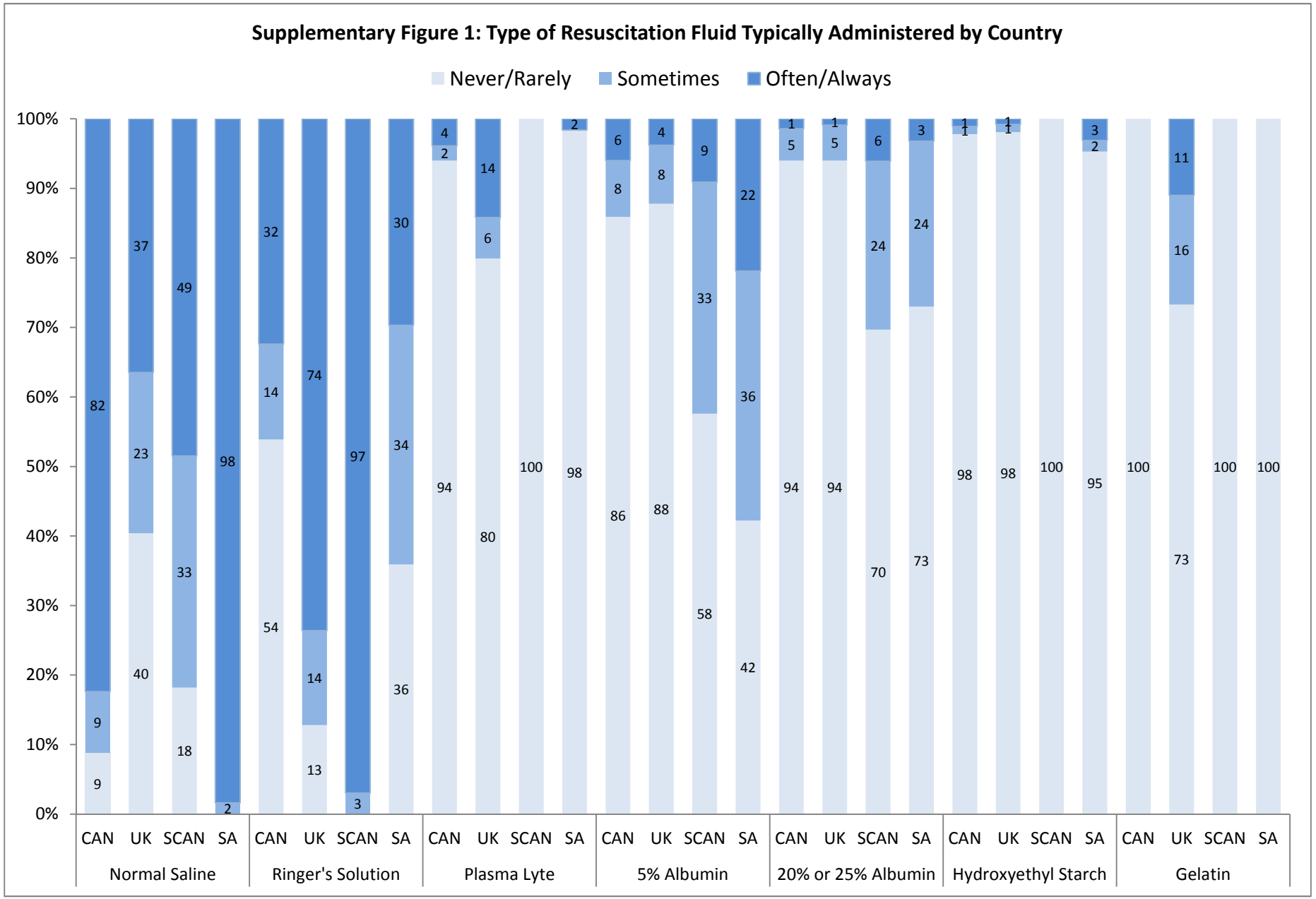
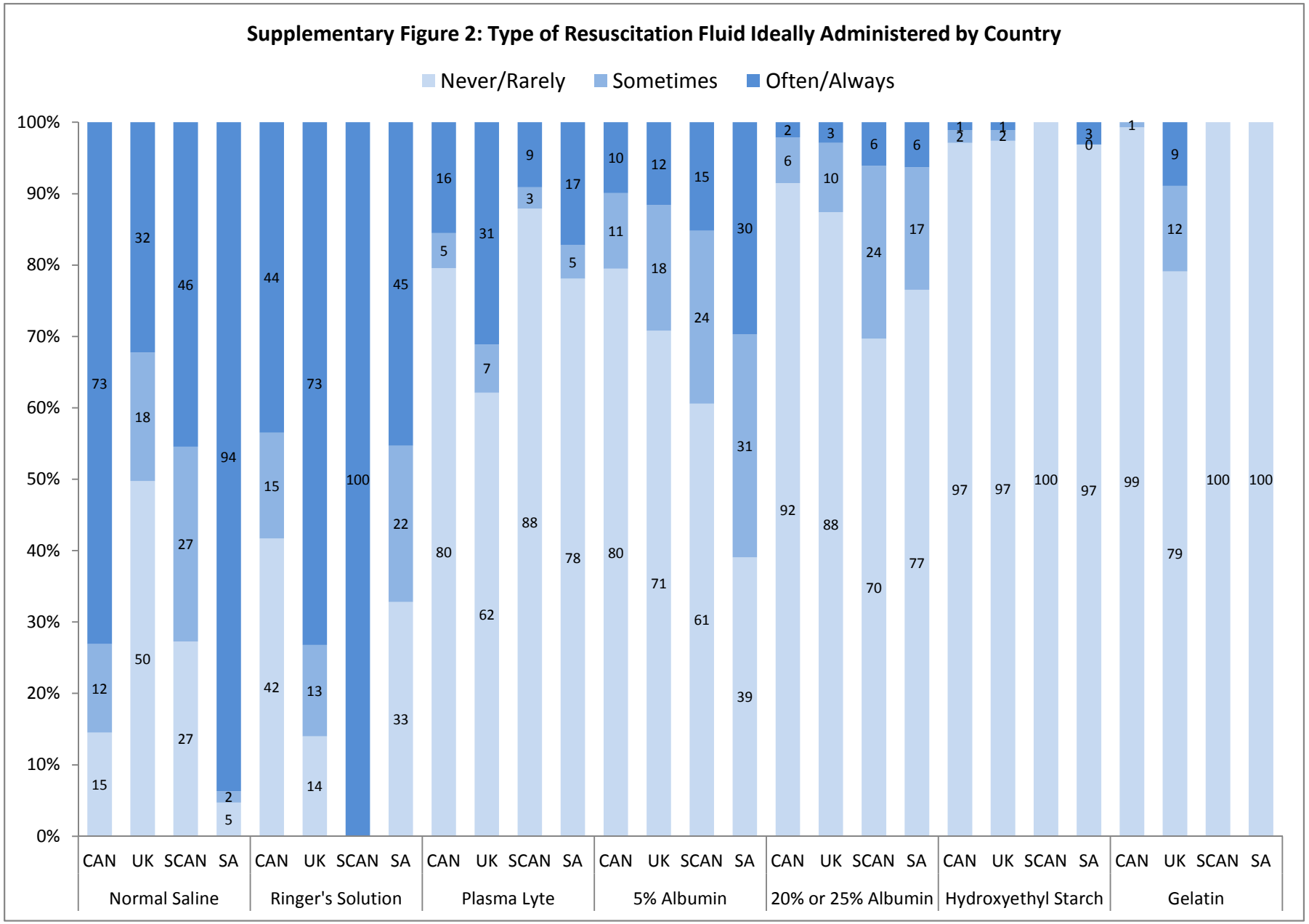


Figure 2: Type of Resuscitation Fluid Ideally Administered by All Respondents, Critical Care and Emergency Physicians







Supplementary Table 1: Summary of Absolute Differences in Proportions (and 95% Confidence Intervals) for Comparisons of Typical versus Ideal Fluid Type Among and Between Emergency and Critical Care Physicians

All Respondents: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	556/1047 (53.1)	496/1045 (47.5)	5.6 (4.0, 7.2)
Ringer's Solutions	632/1045 (60.5)	671/1044 (64.3)	-3.8 (-5.9, -1.6)
Plasma-Lyte	106/1045 (10.1)	264/1043 (25.3)	-15.2 (-17.5, -12.9)
5% Albumin	59/1045 (5.6)	129/1044 (12.4)	-6.7 (-8.3, -5.0)
20-25% Albumin	14/1044 (1.3)	31/1043 (3.0)	-1.6 (-2.6, -0.7)
Hydroxyethyl Starch	10/1044 (1.0)	12/1044 (1.1)	-0.2 (-0.7, 0.3)
Gelatins	73/1045 (7.0)	59/1044 (5.7)	1.3 (0.3, 2.4)
Critical Care Physicians: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	150/537 (27.9)	123/537 (22.9)	5.0 (2.7, 7.3)
Ringer's Solutions	437/537 (81.4)	430/537 (80.1)	1.3 (-1.5, 4.1)
Plasma-Lyte	82/537 (15.3)	196/537 (36.5)	-21.2 (-24.9, -17.6)
5% Albumin	57/537 (10.6)	110/537 (20.5)	-9.9 (-12.6, -7.1)
20-25% Albumin	13/537 (2.4)	24/537 (4.5)	-2.1 (-3.6, -0.5)
Hydroxyethyl Starch	8/537 (1.5)	9/537 (1.7)	-0.2 (-1.0, 0.6)
Gelatins	66/537 (12.3)	53/537 (9.9)	2.4 (0.5, 4.3)
Emergency Physicians: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	376/448 (83.9)	346/448 (77.2)	6.7 (4.2, 9.2)
Ringer's Solutions	158/448 (35.3)	202/448 (45.1)	-9.8 (-13.3, -6.4)
Plasma-Lyte	13/448 (2.9)	51/448 (11.4)	-8.5 (-11.2, -5.8)
5% Albumin	1/448 (0.2)	17/448 (3.8)	-3.6 (-5.3, -1.9)
20-25% Albumin	0/448 (0)	5/448 (1.1)	-1.1 (-2.1, -0.1)
Hydroxyethyl Starch	1/448 (0.2)	3/448 (0.7)	-0.5 (-1.1, 0.2)
Gelatins	2/448 (0.4)	3/448 (0.7)	-0.2 (-0.7, 0.2)
Typical Use: Emergency Physicians versus Critical Care Physicians			
Fluid Type	**Emergency**	**Critical Care**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	376/448 (83.9)	150/537 (27.9)	56 (50.9, 61.1)
Ringer's Solutions	158/448 (35.3)	437/537 (81.4)	-46.1 (-51.6, -40.6)
Plasma-Lyte	13/448 (2.9)	82/537 (15.3)	-12.4 (-15.8, -8.9)
5% Albumin	1/448 (0.2)	57/537 (10.6)	-10.4 (-13.0, -7.8)
20-25% Albumin	0/448 (0)	13/537 (2.4)	-2.4 (-3.7, -1.1)
Hydroxyethyl Starch	1/448 (0.2)	8/537 (1.5)	-1.3 (-2.4, -0.2)
Gelatins	2/448 (0.4)	66/537 (12.3)	-11.8 (-14.7, -9.0)
Ideal Use: Emergency Physicians versus Critical Care Physicians			
Fluid Type	**Emergency**	**Critical Care**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	346/448 (77.2)	123/537 (22.9)	54.3 (49.1, 59.6)
Ringer's Solutions	202/448 (45.1)	430/537 (80.1)	-35.0 (-40.7, -29.3)
Plasma-Lyte	51/448 (11.4)	196/537 (36.5)	-25.1 (-30.1, -20.1)
5% Albumin	17/448 (3.8)	110/537 (20.5)	-16.7 (-20.5, -12.8)
20-25% Albumin	5/448 (1.1)	24/537 (4.5)	-3.4 (-5.4, -1.4)
Hydroxyethyl Starch	3/448 (0.7)	9/537 (1.7)	-1.0 (-2.3, 0.3)
Gelatins	3/448 (0.7)	53/537 (9.9)	-9.2 (-11.8, -6.6)

Supplementary Table 2: Type of Resuscitation Fluid Typically and Ideally Administered by Country

	Typical				Ideal		
Canada	Never/Rarely	Sometimes	Often/Always	**Canada**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=284)	25 (8.8)	25 (8.8)	234 (82.4)	Normal Saline (n=283)	41 (14.5)	35 (12.4)	207 (73.1)
Ringer's Solution (n=284)	153 (53.9)	39 (13.7)	92 (32.4)	Ringer's Solution (n=283)	118 (41.7)	42 (14.8)	123 (43.5)
Plasma Lyte (n=284)	267 (94)	6 (2.1)	11 (3.9)	Plasma Lyte (n=283)	225 (79.5)	14 (4.9)	44 (15.5)
5% Albumin (n=284)	244 (85.9)	23 (8.1)	17 (6)	5% Albumin (n=283)	225 (79.5)	30 (10.6)	28 (9.9)
20% or 25% Albumin (n=284)	267 (94)	13 (4.6)	4 (1.4)	20% or 25% Albumin (n=283)	259 (91.5)	18 (6.4)	6 (2.1)
Hydroxyethyl Starch (n=283)	277 (97.9)	3 (1.1)	3 (1.1)	Hydroxyethyl Starch (n=283)	275 (97.2)	5 (1.8)	3 (1.1)
Gelatin (n=284)	284 (100)	0 (0)	0 (0)	Gelatin (n=283)	281 (99.3)	2 (0.7)	0 (0)
UK	Never/Rarely	Sometimes	Often/Always	**UK**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=666)	269 (40.4)	154 (23.1)	243 (36.5)	Normal Saline (n=665)	331 (49.8)	120 (18)	214 (32.2)
Ringer's Solution (n=664)	85 (12.8)	90 (13.6)	489 (73.6)	Ringer's Solution (n=664)	93 (14)	85 (12.8)	486 (73.2)
Plasma Lyte (n=664)	531 (80)	39 (5.9)	94 (14.2)	Plasma Lyte (n=663)	412 (62.1)	45 (6.8)	206 (31.1)
5% Albumin (n=664)	583 (87.8)	56 (8.4)	25 (3.8)	5% Albumin (n=664)	470 (70.8)	117 (17.6)	77 (11.6)
20% or 25% Albumin (n=664)	624 (94)	34 (5.1)	6 (0.9)	20% or 25% Albumin (n=663)	580 (87.5)	64 (9.7)	19 (2.9)
Hydroxyethyl Starch (n=664)	652 (98.2)	7 (1.1)	5 (0.8)	Hydroxyethyl Starch (n=664)	647 (97.4)	10 (1.5)	7 (1.1)
Gelatin (n=664)	487 (73.3)	104 (15.7)	73 (11)	Gelatin (n=664)	525 (79.1)	80 (12)	59 (8.9)
Scandinavia	Never/Rarely	Sometimes	Often/Always	**Scandinavia**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=33)	6 (18.2)	11 (33.3)	16 (48.5)	Normal Saline (n=33)	9 (27.3)	9 (27.3)	15 (45.5)
Ringer's Solution (n=33)	0 (0)	1 (3)	32 (97)	Ringer's Solution (n=33)	0 (0)	0 (0)	33 (100)
Plasma Lyte (n=33)	33 (100)	0 (0)	0 (0)	Plasma Lyte (n=33)	29 (87.9)	1 (3)	3 (9.1)
5% Albumin (n=33)	19 (57.6)	11 (33.3)	3 (9.1)	5% Albumin (n=33)	20 (60.6)	8 (24.2)	5 (15.2)
20% or 25% Albumin (n=33)	23 (69.7)	8 (24.2)	2 (6.1)	20% or 25% Albumin (n=33)	23 (69.7)	8 (24.2)	2 (6.1)
Hydroxyethyl Starch (n=33)	33 (100)	0 (0)	0 (0)	Hydroxyethyl Starch (n=33)	33 (100)	0 (0)	0 (0)
Gelatin (n=33)	33 (100)	0 (0)	0 (0)	Gelatin (n=33)	33 (100)	0 (0)	0 (0)
Saudi Arabia	Never/Rarely	Sometimes	Often/Always	**Saudi Arabia**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=64)	0 (0)	1 (1.6)	63 (98.4)	Normal Saline (n=64)	3 (4.7)	1 (1.6)	60 (93.8)
Ringer's Solution (n=64)	23 (35.9)	22 (34.4)	19 (29.7)	Ringer's Solution (n=64)	21 (32.8)	14 (21.9)	29 (45.3)
Plasma Lyte (n=64)	63 (98.4)	0 (0)	1 (1.6)	Plasma Lyte (n=64)	50 (78.1)	3 (4.7)	11 (17.2)
5% Albumin (n=64)	27 (42.2)	23 (35.9)	14 (21.9)	5% Albumin (n=64)	25 (39.1)	20 (31.3)	19 (29.7)
20% or 25% Albumin (n=63)	46 (73)	15 (23.8)	2 (3.2)	20% or 25% Albumin (n=64)	49 (76.6)	11 (17.2)	4 (6.3)
Hydroxyethyl Starch (n=64)	61 (95.3)	1 (1.6)	2 (3.1)	Hydroxyethyl Starch (n=64)	62 (96.9)	0 (0)	2 (3.1)
Gelatin (n=64)	64 (100)	0 (0)	0 (0)	Gelatin (n=64)	64 (100)	0 (0)	0 (0)

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A Multi-Country Survey of Emergency and Critical Care Medicine Physicians' Fluid Resuscitation Practices for Adult Patients with Early Septic Shock

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ABSTRACT:

Objectives:

Evidence to guide fluid resuscitation evidence in sepsis continues to evolve. We conducted a multi-country survey of emergency and critical care physicians to describe current stated practice and practice variation related to the quantity, rapidity and type of resuscitation fluid administered in early septic shock to inform the design of future septic shock fluid resuscitation trials.

Methods:

Using a web-based survey tool, we invited critical care and emergency physicians in Canada, the United Kingdom, Scandinavia, and Saudi Arabia to complete a self-administered electronic survey.

Results:

A total of 1097 physicians' responses were included. One litre was the most frequent quantity of resuscitation fluid physicians indicated they would administer at a time (46.9%, n=499). Most (63.0%, n=671) stated that they would administer the fluid challenges as quickly as possible. Overall, normal saline and Ringer's solutions were the preferred crystalloid fluids used 'often' or 'always' in 53.1% (n=556) and 60.5% (n=632) of instances, respectively. However, emergency physicians indicated they would use normal saline 'often' or 'always' in 83.9% (n=376) of instances while critical care physicians said they would use saline 'often' or 'always' in 27.9% (n=150) of instances. Only 1.0% (n=10) of respondents indicated they would use hydroxyethyl starch 'often' or 'always'; use of 5% (5.6% (n=59)) or 20-25% albumin (1.3% (n=14)) was also infrequent. The majority (88.4%, n=896) of respondents indicated that a large randomized controlled trial comparing 5% albumin to a crystalloid fluid in early septic shock was important to conduct.

Conclusions:

Critical care and emergency physicians stated that they rapidly infuse volumes of 500 – 1000 mls of resuscitation fluid in early septic shock. Colloid use, specifically the use of albumin, was

infrequently reported. Our survey identifies the need to conduct a trial on the efficacy of albumin and crystalloids on 90-day mortality in patients with early septic shock.

Study Strengths and Limitations:

- This survey included a large sample of emergency and critical care physicians stated early septic shock resuscitation practices from Canada, the United Kingdom, Scandinavia, and Saudi Arabia
- The survey was designed to be short, simple, and specific to the early resuscitative phase of septic shock so that it would take at most 5 minutes to complete.
- Since the survey focused on the early resuscitative phase of septic shock, the responses to questions may not be generalizable to later phases of septic shock or specific sub populations of patients with septic shock.
- Due to the variable methods used for survey distribution, we could not summarize an accurate response proportion.

BACKGROUND:

Fluid resuscitation is a vital, first line intervention for all patients with septic shock. Management guidelines recommend rapid administration of resuscitation fluid to achieve a minimum of 30 ml/kg in the early hours of resuscitation, with the goal of regaining hemodynamic stability, optimizing organ perfusion and ultimately, improving outcomes and preventing death[1]. While fluid resuscitation is a life-saving intervention, until recently, high quality evidence to guide fluid choice and resuscitation practices has been lacking.

In recent years there has been an accumulation of evidence regarding fluid resuscitation that has served both to change practice and prompt further resuscitation research questions. For example, a multi-centre pediatric trial from East Africa of predominantly malaria-infected children with severe fever and hypoperfusion questioned how aggressively we should administer resuscitation fluids in this setting [2]. This trial found that fluid boluses, as compared to the administration of intravenous maintenance fluids, increased the risk of death at 48 hours. The results of these research findings have encouraged other investigators to further study aggressive versus conservative fluid resuscitation strategies for children and adults with septic shock in the emergency department and intensive care unit and clinical trials are ongoing or recently completed (Clinical Trials.gov NCT02079402 and NCT01973907, respectively). Evidence has also emerged to help guide practice with regard to the use of colloid fluids in sepsis. In 2004, our group conducted a survey of early septic shock resuscitation practices of Canadian critical care physicians and found that hydroxyethyl starch (HES) fluid was used commonly, reportedly 51% of the time[3]. An international cross-sectional study of fluid resuscitation episodes in the intensive care unit conducted in 2007 also documented frequent colloid fluid use (48% of episodes) and 44% of colloids administered were HES fluids[4]. Since the publication of these studies, data from randomized trials and systematic reviews have demonstrated clear harms caused by HES in critically ill patients, particularly those with sepsis[5-9]. Although a recent systematic review of albumin in sepsis found no overall mortality benefit[10], two sub group analyses from recent randomized trials comparing albumin to

crystalloid fluid in the critically ill and severe sepsis and septic shock found reductions in mortality at 28 and 90 days respectively [11,12].

In the context of evolving literature to guide practice, we conducted an early septic shock fluid resuscitation survey to inform the design and provide justification for future early septic shock fluid resuscitation trials comparing 5% albumin versus crystalloid fluid on 90-day mortality. Our survey had two objectives: 1) to describe practice variation among emergency and critical care physicians regarding the quantity, rapidity and type of fluid administered during early septic shock resuscitation and 2) to elicit views of a future early septic shock fluid resuscitation trial comparing 5% albumin versus crystalloid fluid on 90-day mortality by eliciting from respondents the minimal clinically important difference between fluid intervention and control arms that would inform their practice, as well understanding the perceived importance of and respondents' willingness to enroll into such a future trial.

METHODS:

Identification of Study Participants and Survey Distribution:

Our target population consisted of critical care and emergency physicians in Canada, the United Kingdom, Scandinavia, and Saudi Arabia who provide care for adults patients (≥ 18 years of age) with septic shock. These countries were selected because research and opinion leaders in these countries had expressed interest in collaborating on an international trial on early fluid resuscitation.

Participants were contacted by their respective critical care or emergency medicine professional societies in the United Kingdom and Canada, and through direct contact with lead site investigators in Canada, Scandinavia (including the countries Norway, Sweden, Finland and Denmark), and Saudi Arabia using a standardized email containing a web link to the survey. Respondents activated the web link and completed the survey instrument online. The survey was distributed in January and February 2014. To maximize responses, non-respondents received up to two email reminders.

Survey Development:

We generated items for the survey instrument through literature review and consultation with international investigators representing emergency and critical care medicine. Items were reduced and formatted to reduce respondent burden and maximize the response rate. The survey was pilot tested by our investigative team and critical care research fellows at the University of Ottawa in Ottawa, Canada for clinical sensibility and with a target time to completion of 5 minutes. The survey was structured using a web based survey platform (FluidSurveys). Research ethics board approval was sought as required by lead investigators for each country that participated in the survey.

Survey Content:

The survey presented a typical patient with early septic shock in the emergency department(ED); see survey, Supplementary Appendix I. This patient was introduced as a 55-year old 70 Kg female who had just arrived in the ED with suspected septic shock. She was confused, with a blood pressure of 70/30, heart rate 135 beats per minute, respiratory rate of 25 breaths per minute, temperature 39.5 degrees Celsius and oxygen saturation of 96% on 3 litres by nasal prongs. She had already received a total of 1 liter of normal saline over 15 minutes in the ED.

Respondents were then asked a series of questions: the first was to document the quantity and rapidity of fluid administration, and the second question examined the type of resuscitation fluids that they would use in both a "typical" and an "ideal" situation to resuscitate the patient described above. An "ideal" situation was proposed for respondents to ascertain the fluid type given that a physician may wish to give a fluid but that fluid may not be readily available to them in practice (e.g., fluid not stocked or immediately available in the department). For each of these questions, respondents answered based on a 5 point Likert scale (i.e., never, rarely, sometimes, often, always). For the type of resuscitation fluid question (survey questions 2a and 2b), Ringer's solutions (i.e., Ringer's Lactate, Ringer's Acetate, and Hartmann's) were bundled together as one response option, reflecting their biochemical similarity [13] and reducing respondent question burden.

To inform the design of an early septic shock fluid resuscitation trial comparing 5% albumin to a crystalloid fluid on the primary outcome of 90-day mortality, we asked respondents to provide their views on an estimate of the minimal clinically important difference between the fluid intervention and control arms that would be required to inform their practice (response options: 1%, 2.5%, 5%, 7.5%, and 10%). Two further questions were posed to determine the perceived importance of (response options: not at all important, not very important, somewhat important, important, very important) and their willingness to enroll patients into such a trial (response options: yes, no).

We also documented respondents' primary specialty and their practice experience in emergency medicine and/or critical care.

Survey Data Collection and Analysis:

All data were collected electronically through FluidSurveys (Ottawa, ON) and were housed and managed on FluidSurveys'secure servers. Prior to analysis, raw data was exported to Microsoft Excel (Version 2010, Redmond, WA) for cleaning and then exported to SAS (Version 9.2, by SAS Institute Inc., Cary, NC) for analysis.

All data are presented with numbers and proportions for dichotomous and categorical variables, and with means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, as appropriate. Missing responses were not imputed. The 5 point Likert scale responses were combined into 'often or always', 'sometimes', and 'rarely or never' for purposes of data presentation. The data for all respondents were also described according to whether respondents were critical care or emergency medicine physicians. No sample size was calculated *apriori* because as the main survey intent was descriptive. Post - hoc, we calculated absolute differences in proportions and 95 percent confidence intervals (CI) between typical and ideal fluid use for all respondents and by primary specialty (critical care physicians and emergency physicians) respectively. Differences in proportions with 95% CIs for emergency and critical care physicians for typical and ideal fluid were also calculated.

RESULTS:

Study Sample:

A total of 1139 physicians responded to the survey; 16 respondents were not emergency or critical care physicians, a further 15 did not provide care for adult patients with septic shock, and 11 physicians did not respond to one (n = 10) or both (n = 1) of these questions. Thus, a total of 1097 physicians' responses were included in the final results. Of these, 64% (n = 702) were from the United Kingdom, 26% (n = 290) were from Canada, and the remaining 10% (n = 105) were from Saudi Arabi (6.6%, n = 72) and Scandinavia (3.0%, n = 33).

Demographics and Training:

A total of 90% (n = 985) of physicians responded to the primary specialty question. Of these responses, 45.5% (n = 448) of physicians indicated that their primary specialty was emergency medicine. The average number of years spent in clinical practice was 10 (SD = 8).

Quantity and Rapidity of Administration of Resuscitation Fluids:

When we asked physicians about the quantity of resuscitation fluid that they would typically administer at a time to our hypothetical patient with early septic shock in the emergency department, the most common answer was one litre of fluid (46.9%, n = 499), followed by 500 ml (32.0%, n = 340) (see Table 1). When examined by primary specialty, one litre (62.3%, n = 279) and 500 ml (41.5%, n = 223) were the most frequent responses for emergency and critical care physicians, respectively. Most physicians (63%, n = 671) stated that they would administer the fluid challenges as quickly as possible; this response remained the most frequent when the data were examined by emergency and critical care physicians (73.2%, n = 328 and 56.4%, n = 303, respectively).

Table 1: Quantity and Rapidity of Fluid Resuscitation by All Respondents, Critical Care and Emergency Physicians

Quantity n (%)		Rapidity n (%)	
All Respondents			
(n=1064)		**(n=1065)**	
100 mls	2 (0.2)	5 mins	66 (6.2)
250 mls	123 (11.6)	10 mins	98 (9.2)
500 mls	340 (32.0)	15 mins	131 (12.3)
750 mls	9 (0.8)	30 mins	81 (7.6)
1000 mls	499 (46.9)	1 hour	18 (1.7)
Other	91 (8.6)	As quickly as possible	671 (63.0)
Critical Care Physicians			
(n=537)		**(n=537)**	
100 mls	2 (0.4)	5 mins	45 (8.4)
250 mls	86 (16.0)	10 mins	64 (11.9)
500 mls	223 (41.5)	15 mins	75 (14.0)
750 mls	6 (1.1)	30 mins	42 (7.8)
1000 mls	194 (36.1)	1 hour	8 (1.5)
Other	26 (4.8)	As quickly as possible	303 (56.4)
Emergency Physicians			

(n=448)		(n=448)	
100 mls	0 (0)	5 mins	12 (2.7)
250 mls	21 (4.7)	10 mins	25 (5.6)
500 mls	90 (20.1)	15 mins	43 (9.6)
750 mls	3 (0.7)	30 mins	35 (7.8)
1000 mls	279 (62.3)	1 hour	5 (1.1)
Other	55 (12.3)	As quickly as possible	328 (73.2)

Type of Resuscitation Fluid Typically and Ideally Administered:

Normal saline and Ringer's solutions were used typically 'often' or ' always' for early septic shock resuscitation 53.1% (n=556) and 60.5% (n=632) of the time, respectively (see Figure 1 and Table 2). In contrast, respondents infrequently used Plasma-Lyte (10.1%, n=106), 5% albumin (5.6%, n=59), 20-25% albumin (1.3%, n=14), and gelatins (7.0%, n=73) 'often' or 'always' in early resuscitative efforts. Only 1.0% (n=10) of respondents indicated they would use hydroxyethyl starch 'often' or 'always' in the resuscitative phase of septic shock.

When asked about the use of these fluids in the ideal setting where they would be immediately available, use of Plasma-Lyte and 5% albumin 'often' or 'always' increased the most (Plasma-Lyte from 10.1% (n = 106) to 25.3% (n = 264) (absolute difference (AD) = -15.2%; 95% CI: -17.5% to -12.9%) and 5% albumin from 5.6% (n = 59) to 12.4% (n = 129) (AD = -6.7%; 95% CI: -8.3% to -5.0%) (see Figure 2 and Supplementary Table 1).

When the typical use of crystalloid fluids was examined by primary specialty, emergency physicians indicated they would use normal saline 'often' or 'always' 83.9% (n = 376) in contrast to critical care physicians who said they would use saline 27.9% (n = 150) (AD = 56.0%; 95% CI: 50.9% to 61.1%) (see Figure 1 and Supplementary Table 1). In the ideal setting, where these fluids would be immediately available, the two fluid type responses that increased the most for emergency physicians were Ringer's solutions from 35.3% (n = 158) to 45.1% (n = 202) (AD = -9.8; 95% CI: -13.3 to -6.4) and Plasma-Lyte from 2.9% (n = 13) to 11.4% (n = 51) (AD = -8.5; 95% CI: -11.2 to -5.8)) (see Figure 2, Supplementary Table 1). The two fluid type responses that increased the most in the ideal setting for critical care physicians were Plasma-Lyte (from 15.3%

(n = 82) to 36.5% (n = 196), AD = -21.2; 95% CI: -24.9 to -17.6)) and 5% albumin (from 10.6% (n = 57) to 20.5% (n = 110), AD = -9.9; 95% CI: -12.6 to -7.1)).

A summary of typical and ideal fluid use by country is provided in Supplementary Table 2 and Supplementary Figures 1 and 2 respectively.

Table 2: Type of Resuscitation Fluid Typically & Ideally Administered by All Respondents, Critical Care and Emergency Physicians

	Typically Administered				Ideally Administered			
Type	Number Respondents	Never/Rarely n (%)	Sometimes n (%)	Often/Always n (%)	Number Respondents	Never/Rarely n (%)	Sometimes n (%)	Often/Always n (%)
All Respondents								
Normal Saline	(n = 1047)	300 (28.7)	191 (18.2)	556 (53.1)	(n = 1045)	384 (36.7)	165 (15.8)	496 (47.5)
Ringer's Solutions	(n = 1045)	261 (25.0)	152 (14.5)	632 (60.5)	(n = 1044)	232 (22.2)	141 (13.5)	671 (64.3)
Plasma-Lyte	(n = 1045)	894 (85.6)	45 (4.3)	106 (10.1)	(n = 1043)	716 (68.7)	63 (6.0)	264 (25.3)
5% Albumin	(n = 1045)	873 (83.5)	113 (10.8)	59 (5.6)	(n = 1044)	740 (70.9)	175 (16.8)	129 (12.4)
20% or 25% Albumin	(n = 1044)	960 (92.0)	70 (6.7)	14 (1.3)	(n = 1043)	911 (87.3)	101 (9.7)	31 (3.0)
Hydroxyethyl Starch	(n = 1044)	1023 (98.0)	11 (1.1)	10 (1.0)	(n = 1044)	1017 (97.4)	15 (1.4)	12 (1.1)
Gelatin	(n = 1045)	868 (83.1)	104 (10.0)	73 (7.0)	(n = 1044)	903 (86.5)	82 (7.9)	59 (5.7)
Critical Care Physicians								
Normal Saline	(n = 537)	249 (46.4)	138 (25.7)	150 (27.9)	(n = 537)	300 (55.9)	114 (21.2)	123 (22.9)
Ringer's Solutions	(n = 537)	35 (6.5)	65 (12.1)	437 (81.4)	(n = 537)	51 (9.5)	56 (10.4)	430 (80.1)
Plasma-Lyte	(n = 537)	426 (79.3)	29 (5.4)	82 (15.3)	(n = 537)	297 (55.3)	44 (8.2)	196 (36.5)
5% Albumin	(n = 537)	383 (71.3)	97 (18.1)	57 (10.6)	(n = 537)	310 (57.7)	117 (21.8)	110 (20.5)
20% or 25% Albumin	(n = 537)	466(86.8)	58 (10.8)	13 (2.4)	(n = 537)	442 (82.3)	71 (13.2)	24 (4.5)
Hydroxyethyl Starch	(n = 537)	522 (97.2)	7 (1.3)	8 (1.5)	(n = 537)	521 (97.0)	7 (1.3)	9 (1.7)
Gelatin	(n = 537)	394 (73.4)	77 (14.3)	66 (12.3)	(n = 537)	426 (79.3)	58 (10.8)	53 (9.9)
Emergency Physicians								
Normal Saline	(n = 448)	28 (6.3)	44 (9.8)	376 (83.9)	(n = 448)	61 (13.6)	41 (9.2)	346 (77.2)
Ringer's Solutions	(n = 448)	211 (47.1)	79 (17.6)	158 (35.3)	(n = 448)	170 (37.9)	76 (17.0)	202 (45.1)
Plasma-Lyte	(n = 448)	422 (94.2)	13 (2.9)	13 (2.9)	(n = 448)	381 (85.0)	16 (3.6)	51 (11.4)
5% Albumin	(n = 448)	434 (96.9)	13 (2.9)	1 (0.2)	(n = 448)	384 (85.7)	47 (10.5)	17 (3.8)
20% or 25% Albumin	(n = 448)	441 (98.4)	7 (1.6)	0 (0)	(n = 448)	423 (94.4)	20 (4.5)	5 (1.1)
Hydroxyethyl Starch	(n = 448)	444 (99.1)	3 (0.7)	1 (0.2)	(n = 448)	437 (97.5)	8 (1.8)	3 (0.7)
Gelatin	(n = 448)	425 (94.9)	21 (4.7)	2 (0.4)	(n = 448)	424 (94.6)	21 (4.7)	3 (0.7)

Views on a Future Early Septic Shock Fluid Resuscitation Trial

Most respondents indicated that the minimal clinically important difference (MCID) for a future trial comparing 5% albumin and a crystalloid fluid on 90-day mortality for early septic shock that would be required to maintain or change their practise was 5% (53.6%, 539/1005). Respondents also indicated that a large randomized controlled trial comparing 5% albumin to a crystalloid fluid with a primary outcome of 90-day mortality was important to conduct as 88.4% (896/1014) of respondents indicated the trial was somewhat important (24.0%,243/1014), important (39.4%, 400/1014), or very important (25%,253/1014). Furthermore, 84.4% (851/1008) of respondents indicated that they would be willing to enroll patients into such a future clinical trial.

DISCUSSION:

Results of our multi-country survey suggest that emergency and critical care physicians who assess and manage adult patients in the early resuscitative phase of septic shock prefer that fluid challenges (at least 500 mls) be administered as quickly as possible. When examined by primary specialty, critical care physicians indicated a preference to use Ringer's solutions compared to emergency physicians who indicated a preference to use normal saline. Although the reported use of Plasma-Lyte was infrequent, our survey data suggest that both emergency and critical care physicians would use more of this crystalloid fluid if it was readily available to them. Use of hydroxyethyl starch fluid was uncommon and the reported use of albumin (5% or 20-25%) was infrequent, although critical care physicians also indicated that they would use albumin more frequently if it was immediately available to them.

An abundance of observational evidence from large propensity-matched cohort studies in the surgical[14,15] and critically ill[16] populations, and a prospective sequential period study[17] in the critically ill suggest that high-chloride fluids (e.g., normal saline) may be associated with excess mortality compared to lower-chloride fluids such as Ringer's solutions or Plasma-Lyte. In addition, normal saline resuscitation has been associated with the subsequent use of renal replacement therapy, increased post-operative infections, and prolonged length of stay in

hospital[14-17]. A recently published pilot trial examined normal saline versus Plasma-Lyte for fluid resuscitation in the intensive care unit[18]. Investigators did not detect an increased risk of acute kidney injury or failure, or an increased risk of requirement for renal replacement therapy with normal saline. However, the study was underpowered for these clinical outcomes and a larger trial with death as the primary endpoint is now planned (NCT02721654). Our survey, and a similar survey conducted in Scotland[19] suggest that emergency physicians prefer using normal saline, while critical care physicians prefer Ringer's solutions in septic shock. The variability in stated practice between emergency and critical care physicians that was evident in our survey may reflect an absence of high quality evidence to support the preference of either of these fluids, although a recent network meta-analysis of randomized controlled fluid trials in sepsis found balanced crystalloids such as Ringer's or Plasma-Lyte as compared to normal saline were associated with a reduced odds of death[20]. However, since the reported use of both Ringer's solutions and Plasma-Lyte further increased when presented with an 'ideal' but still theoretical scenario in our survey, lack of availability of these fluids or unit-specific policies or protocols[21] may contribute to the reported practice variability we identified.

Very few emergency and critical care physicians indicated that they would use HES boluses in the early resuscitative phase septic shock. This contrasts sharply to a septic shock resuscitation survey from 2004 in which Canadian critical care physicians reported that they would use HES fluids for early septic shock resuscitation 51% of the time. In the European intensive care unit fluid challenge observational study conducted in 2013, hydroxyethyl starch use accounted for only 10.8% of all fluid challenges in the study[21]. This apparent change in practice is likely related to high quality evidence from randomized controlled trials and systematic reviews in the last decade that now confirm starch fluids increase the risk of death and the use of renal replacement therapy in patients with severe sepsis and septic shock[6,7,9].

According to our survey results, the use of albumin in the early septic shock setting also remains infrequent despite the SAFE (A Comparison of Albumin to Saline for Fluid Resuscitation in the Intensive Care Unit) severe sepsis subgroup analysis that suggested 4% albumin compared to normal saline was associated with a significant reduction in 28-day mortality. After

the conduct of this survey in 2014, the ALBIOS trial (Albumin Replacement for Patients with Severe Sepsis and Septic Shock) which compared 20% albumin with crystalloids versus crystalloids alone for patients with severe sepsis and septic shock was published. The ALBIOS trial found a mortality benefit at 90 days for 20% albumin in a post hoc analysis of patients with septic shock but not those with severe sepsis[12]. If practice was influenced by that trial, it is possible that the albumin responses in our survey under-represent current use in early septic shock.

This survey has several weaknesses. A denominator could not be calculated to ascertain a response proportion because of the variable methods we used to distribute the survey. Although we obtained responses from approximately 1000 critical care and emergency medicine physicians from Canada, the United Kingdom, Saudi Arabia and Scandinavia, we cannot confirm that the responses generated are representative of the countries or regions. Resuscitation questions were asked in relation to one hypothetical early septic shock scenario and as such, it is not possible to comment on fluid resuscitation practices according to physician characteristics, for patients in the later phase of septic shock or with specific physiological characteristics (e.g., hypoalbuminemia), or chronic morbidities . However, this survey was large (~1000 responses), and it includes the stated preferences of both critical care and emergency medicine physicians, which are divergent with regard to the quantity and type of resuscitation fluid used for early septic shock resuscitation. Although answers to questions related to other aspects of septic shock management were not obtained, the answers provide robust information regarding the fluid resuscitation practices of a wide variety of physicians managing patients in the early resuscitative phase septic shock. Furthermore, the survey was designed to be brief and take less than 5 minutes to complete to maximize responses to each question. That goal was achieved, since at least 95% of respondents answered each of the resuscitation questions.

In summary, in the resuscitative phase of septic shock, emergency and critical care physician practices as stated in this survey are to administer volumes of resuscitation fluid most commonly in the range of 500 to 1000 mls at a time. It is important to note that these volumes

are within the current surviving sepsis resuscitation guidelines that recommend minimum achievement of 30 ml/kg in the early hours of resuscitation since our aim was to elicit details of how much bolused resuscitation fluid would be administered at a time during early septic shock [1]. Although normal saline and Ringer's solutions are the two most common crystalloid fluids, stated preferences differ between emergency and critical care physicians. Most physicians support a future trial of albumin compared with crystalloid fluid in the early phase of septic shock.

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COMPETING INTERESTS:

FluidSurveys involvement in the project was limited to providing the secure platform that allowed the research team to collect data. AP has received grant support from CSL Behring and Fresenius Kabi and LM has received grant support from CSL Behring, all of which is outside of this submitted work. SMB has consulted for Baxter Healthcare Corp.

DATA SHARING STATEMENT:

There are no additional data to share.

CONTRIBUTORSHIP:

LM, DF, BHR, TW, AG, AP, YA, and JM conceived the survey design. LM drafted the manuscript and all authors contributed to interpretation of the data and critical revisions of the manuscript. All authors have given permission to submit this manuscript for publication.

FIGURE LEGENDS:

Figure 1: The Y-axis depicts the proportion of respondents that answered Never/Rarely, Sometimes, or Often/Always to each typical resuscitation fluid type. The X-axis includes each typical resuscitation fluid type according to all respondents, emergency physicians, and critical care physicians. The response for Ringer's solutions could reflect typical use of Ringer's Lactate, Ringer's Acetate, or Hartmann's solutions, since these solutions were bundled into one response option in survey question 2a. ALL = All respondents, CCP = Critical Care Physicians, EP = Emergency Physicians

Figure 2: The Y-axis depicts the proportion of respondents that answered Never/Rarely, Sometimes, or Often/Always to each ideal resuscitation fluid type. The X-axis includes each ideal resuscitation fluid type according to all respondents, emergency physicians, and critical care physicians. The response for Ringer's solutions could reflect ideal use of Ringer's Lactate, Ringer's Acetate or Hartmann's solutions since these solutions were bundled into one response option in survey question 2b. ALL = All respondents, CCP = Critical Care Physicians, EP = Emergency Physicians

Supplementary Figure 1: The Y-axis depicts the proportion of respondents that answered Never/Rarely, Sometimes, or Often/Always to each typical resuscitation fluid type. The X-axis includes each typical resuscitation fluid type according to physicians in Canada, United Kingdom, Scandinavia, and Saudi Arabia. The response for Ringer's solutions could reflect typical use of Ringer's Lactate, Ringer's Acetate or Hartmann's solutions since these solutions were bundled into one response option in survey question 2a. CAN = Canada, UK = United Kingdom, SCAN = Scandinavia, SA = Saudi Arabia

Supplementary Figure 2: The Y-axis depicts the proportion of respondents that answered Never/Rarely, Sometimes, or Often/Always to each ideal resuscitation fluid type. The X-axis includes each ideal resuscitation fluid type according to physicians in Canada, United Kingdom, Scandinavia, and Saudi Arabia. The response for Ringer's solutions could reflect ideal use of

Ringer's Lactate, Ringer's Acetate or Hartmann's solutions since these solutions were bundled into one response option in survey question 2b. CAN = Canada, UK = United Kingdom, SCAN = Scandinavia, SA = Saudi Arabia

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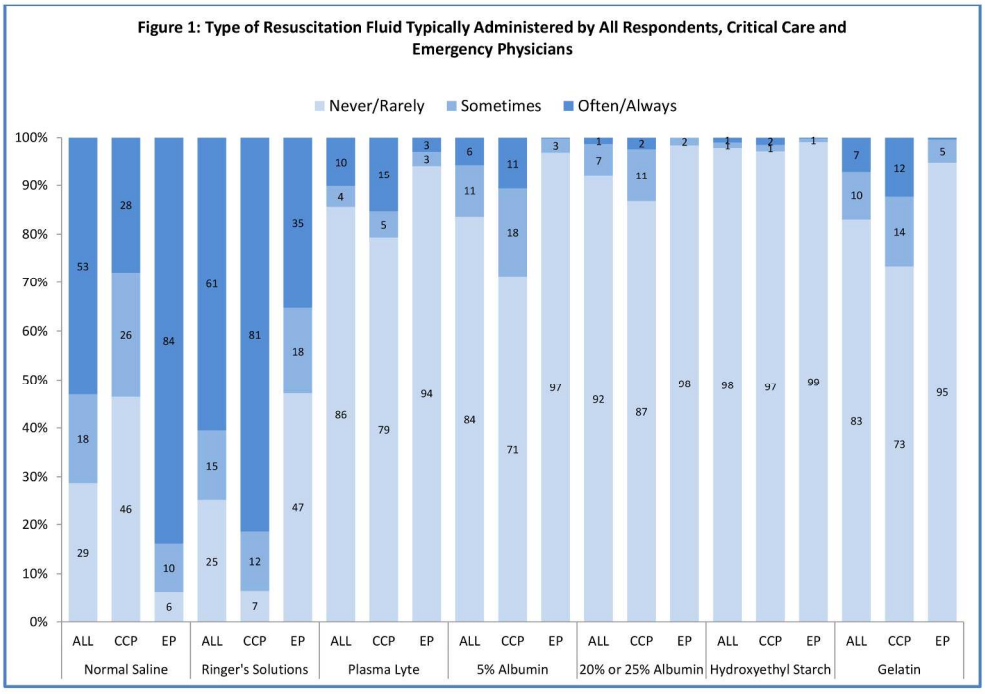

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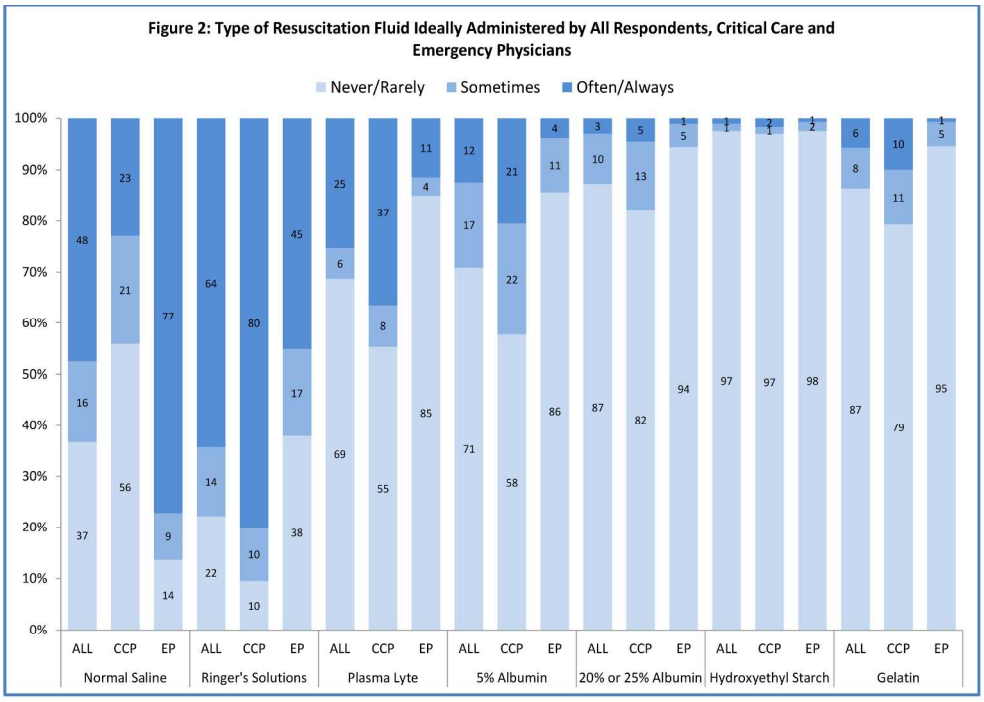

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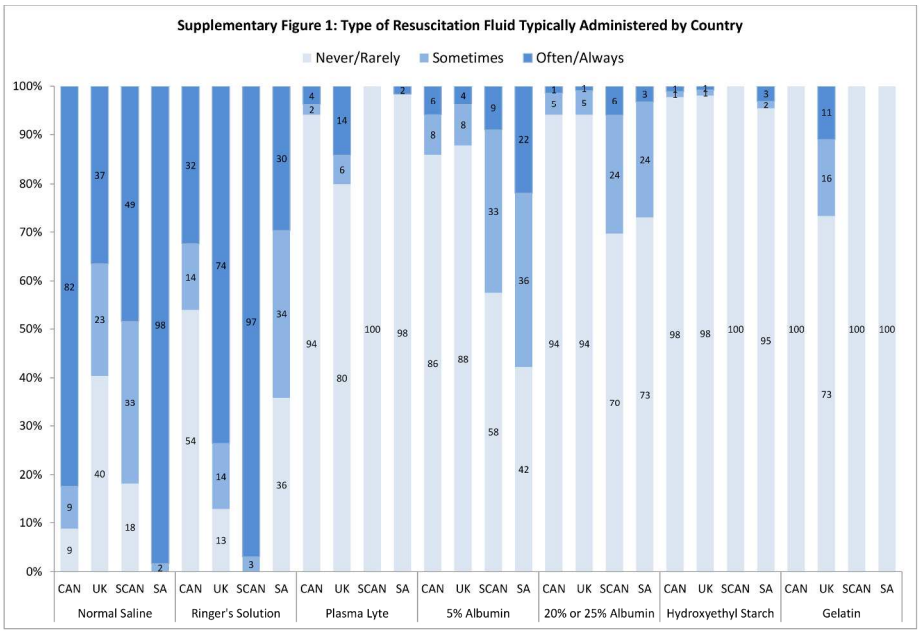

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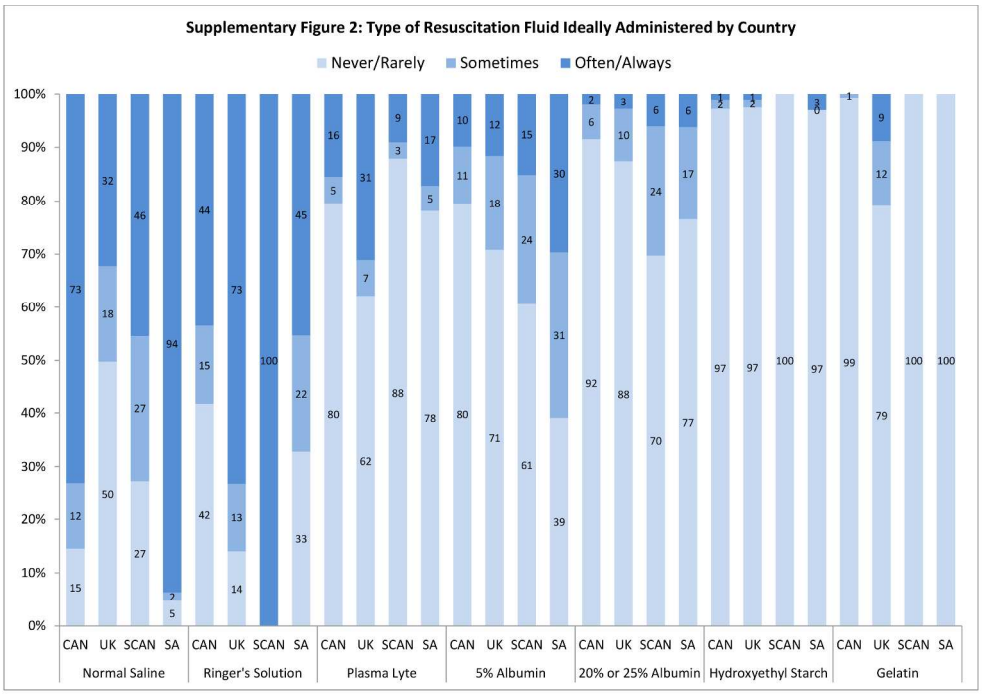

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Supplementary Table 1: Summary of Absolute Differences in Proportions (and 95% Confidence Intervals) for Comparisons of Typical versus Ideal Fluid Type Among and Between Emergency and Critical Care Physicians

All Respondents: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	556/1047 (53.1)	496/1045 (47.5)	5.6 (4.0, 7.2)
Ringer's Solutions	632/1045 (60.5)	671/1044 (64.3)	-3.8 (-5.9, -1.6)
Plasma-Lyte	106/1045 (10.1)	264/1043 (25.3)	-15.2 (-17.5, -12.9)
5% Albumin	59/1045 (5.6)	129/1044 (12.4)	-6.7 (-8.3, -5.0)
20-25% Albumin	14/1044 (1.3)	31/1043 (3.0)	-1.6 (-2.6, -0.7)
Hydroxyethyl Starch	10/1044 (1.0)	12/1044 (1.1)	-0.2 (-0.7, 0.3)
Gelatins	73/1045 (7.0)	59/1044 (5.7)	1.3 (0.3, 2.4)
Critical Care Physicians: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	150/537 (27.9)	123/537 (22.9)	5.0 (2.7, 7.3)
Ringer's Solutions	437/537 (81.4)	430/537 (80.1)	1.3 (-1.5, 4.1)
Plasma-Lyte	82/537 (15.3)	196/537 (36.5)	-21.2 (-24.9, -17.6)
5% Albumin	57/537 (10.6)	110/537 (20.5)	-9.9 (-12.6, -7.1)
20-25% Albumin	13/537 (2.4)	24/537 (4.5)	-2.1 (-3.6, -0.5)
Hydroxyethyl Starch	8/537 (1.5)	9/537 (1.7)	-0.2 (-1.0, 0.6)
Gelatins	66/537 (12.3)	53/537 (9.9)	2.4 (0.5, 4.3)
Emergency Physicians: Typical versus Ideal			
Fluid Type	**Typical**	**Ideal**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	376/448 (83.9)	346/448 (77.2)	6.7 (4.2, 9.2)
Ringer's Solutions	158/448 (35.3)	202/448 (45.1)	-9.8 (-13.3, -6.4)
Plasma-Lyte	13/448 (2.9)	51/448 (11.4)	-8.5 (-11.2, -5.8)
5% Albumin	1/448 (0.2)	17/448 (3.8)	-3.6 (-5.3, -1.9)
20-25% Albumin	0/448 (0)	5/448 (1.1)	-1.1 (-2.1, -0.1)
Hydroxyethyl Starch	1/448 (0.2)	3/448 (0.7)	-0.5 (-1.1, 0.2)
Gelatins	2/448 (0.4)	3/448 (0.7)	-0.2 (-0.7, 0.2)
Typical Use: Emergency Physicians versus Critical Care Physicians			
Fluid Type	**Emergency**	**Critical Care**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	376/448 (83.9)	150/537 (27.9)	56 (50.9, 61.1)
Ringer's Solutions	158/448 (35.3)	437/537 (81.4)	-46.1 (-51.6, -40.6)
Plasma-Lyte	13/448 (2.9)	82/537 (15.3)	-12.4 (-15.8, -8.9)
5% Albumin	1/448 (0.2)	57/537 (10.6)	-10.4 (-13.0, -7.8)
20-25% Albumin	0/448 (0)	13/537 (2.4)	-2.4 (-3.7, -1.1)
Hydroxyethyl Starch	1/448 (0.2)	8/537 (1.5)	-1.3 (-2.4, -0.2)
Gelatins	2/448 (0.4)	66/537 (12.3)	-11.8 (-14.7, -9.0)
Ideal Use: Emergency Physicians versus Critical Care Physicians			
Fluid Type	**Emergency**	**Critical Care**	**Absolute Difference % (95% Confidence Intervals)**
Normal Saline	346/448 (77.2)	123/537 (22.9)	54.3 (49.1, 59.6)
Ringer's Solutions	202/448 (45.1)	430/537 (80.1)	-35.0 (-40.7, -29.3)
Plasma-Lyte	51/448 (11.4)	196/537 (36.5)	-25.1 (-30.1, -20.1)
5% Albumin	17/448 (3.8)	110/537 (20.5)	-16.7 (-20.5, -12.8)
20-25% Albumin	5/448 (1.1)	24/537 (4.5)	-3.4 (-5.4, -1.4)
Hydroxyethyl Starch	3/448 (0.7)	9/537 (1.7)	-1.0 (-2.3, 0.3)
Gelatins	3/448 (0.7)	53/537 (9.9)	-9.2 (-11.8, -6.6)

Supplementary Table 2: Type of Resuscitation Fluid Typically and Ideally Administered by Country

	Typical				Ideal		
Canada	Never/Rarely	Sometimes	Often/Always	**Canada**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=284)	25 (8.8)	25 (8.8)	234 (82.4)	Normal Saline (n=283)	41 (14.5)	35 (12.4)	207 (73.1)
Ringer's Solution (n=284)	153 (53.9)	39 (13.7)	92 (32.4)	Ringer's Solution (n=283)	118 (41.7)	42 (14.8)	123 (43.5)
Plasma Lyte (n=284)	267 (94)	6 (2.1)	11 (3.9)	Plasma Lyte (n=283)	225 (79.5)	14 (4.9)	44 (15.5)
5% Albumin (n=284)	244 (85.9)	23 (8.1)	17 (6)	5% Albumin (n=283)	225 (79.5)	30 (10.6)	28 (9.9)
20% or 25% Albumin (n=284)	267 (94)	13 (4.6)	4 (1.4)	20% or 25% Albumin (n=283)	259 (91.5)	18 (6.4)	6 (2.1)
Hydroxyethyl Starch (n=283)	277 (97.9)	3 (1.1)	3 (1.1)	Hydroxyethyl Starch (n=283)	275 (97.2)	5 (1.8)	3 (1.1)
Gelatin (n=284)	284 (100)	0 (0)	0 (0)	Gelatin (n=283)	281 (99.3)	2 (0.7)	0 (0)
UK	Never/Rarely	Sometimes	Often/Always	**UK**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=666)	269 (40.4)	154 (23.1)	243 (36.5)	Normal Saline (n=665)	331 (49.8)	120 (18)	214 (32.2)
Ringer's Solution (n=664)	85 (12.8)	90 (13.6)	489 (73.6)	Ringer's Solution (n=664)	93 (14)	85 (12.8)	486 (73.2)
Plasma Lyte (n=664)	531 (80)	39 (5.9)	94 (14.2)	Plasma Lyte (n=663)	412 (62.1)	45 (6.8)	206 (31.1)
5% Albumin (n=664)	583 (87.8)	56 (8.4)	25 (3.8)	5% Albumin (n=664)	470 (70.8)	117 (17.6)	77 (11.6)
20% or 25% Albumin (n=664)	624 (94)	34 (5.1)	6 (0.9)	20% or 25% Albumin (n=663)	580 (87.5)	64 (9.7)	19 (2.9)
Hydroxyethyl Starch (n=664)	652 (98.2)	7 (1.1)	5 (0.8)	Hydroxyethyl Starch (n=664)	647 (97.4)	10 (1.5)	7 (1.1)
Gelatin (n=664)	487 (73.3)	104 (15.7)	73 (11)	Gelatin (n=664)	525 (79.1)	80 (12)	59 (8.9)
Scandinavia	Never/Rarely	Sometimes	Often/Always	**Scandinavia**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=33)	6 (18.2)	11 (33.3)	16 (48.5)	Normal Saline (n=33)	9 (27.3)	9 (27.3)	15 (45.5)
Ringer's Solution (n=33)	0 (0)	1 (3)	32 (97)	Ringer's Solution (n=33)	0 (0)	0 (0)	33 (100)
Plasma Lyte (n=33)	33 (100)	0 (0)	0 (0)	Plasma Lyte (n=33)	29 (87.9)	1 (3)	3 (9.1)
5% Albumin (n=33)	19 (57.6)	11 (33.3)	3 (9.1)	5% Albumin (n=33)	20 (60.6)	8 (24.2)	5 (15.2)
20% or 25% Albumin (n=33)	23 (69.7)	8 (24.2)	2 (6.1)	20% or 25% Albumin (n=33)	23 (69.7)	8 (24.2)	2 (6.1)
Hydroxyethyl Starch (n=33)	33 (100)	0 (0)	0 (0)	Hydroxyethyl Starch (n=33)	33 (100)	0 (0)	0 (0)
Gelatin (n=33)	33 (100)	0 (0)	0 (0)	Gelatin (n=33)	33 (100)	0 (0)	0 (0)
Saudi Arabia	Never/Rarely	Sometimes	Often/Always	**Saudi Arabia**	Never/Rarely	Sometimes	Often/Always
Normal Saline (n=64)	0 (0)	1 (1.6)	63 (98.4)	Normal Saline (n=64)	3 (4.7)	1 (1.6)	60 (93.8)
Ringer's Solution (n=64)	23 (35.9)	22 (34.4)	19 (29.7)	Ringer's Solution (n=64)	21 (32.8)	14 (21.9)	29 (45.3)
Plasma Lyte (n=64)	63 (98.4)	0 (0)	1 (1.6)	Plasma Lyte (n=64)	50 (78.1)	3 (4.7)	11 (17.2)
5% Albumin (n=64)	27 (42.2)	23 (35.9)	14 (21.9)	5% Albumin (n=64)	25 (39.1)	20 (31.3)	19 (29.7)
20% or 25% Albumin (n=63)	46 (73)	15 (23.8)	2 (3.2)	20% or 25% Albumin (n=64)	49 (76.6)	11 (17.2)	4 (6.3)
Hydroxyethyl Starch (n=64)	61 (95.3)	1 (1.6)	2 (3.1)	Hydroxyethyl Starch (n=64)	62 (96.9)	0 (0)	2 (3.1)
Gelatin (n=64)	64 (100)	0 (0)	0 (0)	Gelatin (n=64)	64 (100)	0 (0)	0 (0)

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Appendix 1: Early Septic Shock Fluid Resuscitation Survey

This survey is directed to critical care and emergency medicine physicians who primarily care for adult patients.This survey will take less than 5 minutes to complete. All results will be reported in aggregate numbers without personal or institutional identifying information. The Research Ethics Board of the The Ottawa Hospital-Ottawa Hospital Research Institute has approved this study.

Do you practice critical care medicine or emergency medicine?

- ○ Yes
- ○ No

Do you treat adult patients in the intensive care unit or the emergency department?

- ○ Yes
- ○ No

Consider the following scenario: You have been asked to see a 55 year old, 70 Kg female who has just arrived in the emergency department (ED) with suspected septic shock. She is confused, with a blood pressure of 70/30, heart rate 135 beats per minute, respiratory rate of 25 breaths per minute, temperature 39.5 degrees Celsius and oxygen saturation of 96% on 3 liters by nasal prongs. She has already received a total of 1 liter of normal saline over 15 minutes in the emergency department.

(1a) For this patient, how much resuscitation fluid would you typically administer at a time?

- ○ 100 mls
- ○ 250 mls
- ○ 500 mls
- ○ 750 mls
- ○ 1000 mls
- ○ Other quantity, please specify... _____

(1b) For this patient, how fast would you typically administer administer this fluid challenge(s)?

- ○ 5 mins
- ○ 10 mins
- ○ 15 mins
- ○ 30 mins
- ○ 1 hour
- ○ As quickly as possible

(2a) What type(s) of resuscitation fluid do you typically administer during the course of early resuscitation from septic shock?

Please provide an answer for each option

	Never	Rarely	Sometimes	Often	Always
Normal Saline	○	○	○	○	○
Ringers Lactate/Acetate or Hartmanns	○	○	○	○	○
Plasmalyte	○	○	○	○	○
5% Albumin	○	○	○	○	○
20% or 25% Albumin	○	○	○	○	○
Hydroxyethyl Starch	○	○	○	○	○
Gelatin	○	○	○	○	○

(2b) What type(s) of resuscitation fluid would you ideally administer during the course of early resuscitation from septic shock? Imagine that all the fluids are immediately available.

Please provide an answer for each option

	Never	Rarely	Sometimes	Often	Always
Normal Saline	○	○	○	○	○
Ringers Lactate/Acetate or Hartmanns.	○	○	○	○	○
Plasmalyte	○	○	○	○	○
5% Albumin	○	○	○	○	○
20% or 25% Albumin	○	○	○	○	○
Hydroxyethyl Starch	○	○	○	○	○
Gelatin	○	○	○	○	○

The following series of questions pertain to an early septic shock fluid resuscitation randomized controlled trial that we are planning. The trial will ask the following question: Does 5% albumin, compared to a crystalloid fluid reduce 90 day mortality due to septic shock?

(3) What would you consider the minimal clinically important difference (absolute risk difference) between our colloid arm (5% albumin) and crystalloid arm(s) that would change or maintain your practise? To answer this question, assume that 5% albumin is the superior fluid and the baseline risk of death at 90 days is 35%.

- ○ 1%
- ○ 2.5%
- ○ 5%
- ○ 7.5%
- ○ 10%

(4) Would you be willing to enrol patients in a pragmatic international early septic shock fluid resuscitation trial to compare the effectiveness of 5% albumin versus a crystalloid fluid(s) on 90 day mortality?

- ○ Yes
- ○ No

(5) How important is such a trial?

- ○ Very important
- ○ Important
- ○ Somewhat important
- ○ Not very important
- ○ Not at all important

How many years have you been in Intensive Care or Emergency Medicine practice since completing your training?

Please indicate your primary speciality.

- ○ Internal Medicine
- ○ Surgery
- ○ Anesthesia
- ○ Emergency Medicine
- ○ Critical Care
- ○ Other, please specify _____

The following table indicates where Strobe Check List Items are found in the manuscript entitled A Multi-Country Survey of Emergency and Critical Care Medicine Physicians' Fluid Resuscitation Practises for Adult Patients with Early Septic Shock by L. McIntyre et al

Item	Item No	Page(s) in manuscript
Title and Abstract	1	
a		1
b		3
Introduction		
Background/rationale	2	5
Objectives	3	6
Methods		
Study Design	4	6
Setting	5	6-9
Participants	6	6
Variables	7	8, Appendix I
Data sources/measurement	8	Appendix I
Bias	9	Discussed in limitations section (9)
Study Size	10	9*
Quantitative variables	11	9
Statistical methods	12	
a		9
b		N/A
c		9**
d		N/A
e		N/A
Results		
Participants	13	13
a		
b		
c		
Descriptive Data	14	
a		9-10
b		Denominators for all responses presented Table 1, 2, Suppl. Table 1, 2
Main Results	16	10 - 14
a		
b		
c		
Other analyses	17	N/A
Discussion		
Key Results	18	14 – 16

Limitations	19	16
Interpretation	20	16-17
Generalizability	21	16
Other Information		
Funding	22	This study is unfunded.

Legend: N/A = not applicable

*A sentence about the sample size for this quantitative survey has been added to page 9 (revised tracked manuscript is attached)

**A sentence to clarify that missing data was not imputed was added to the statistical methods section on page 9 (revised tracked manuscript is attached)