THE DECISION-MAKING BEHIND A FLUID RESUSCITATION PRESCRIPTION AND THE EVIDENCE-BASED ASSESSMENT TOOLS THAT ARE AVAILABLE TO SUPPORT IT: A MIXED-METHODS STUDY

by

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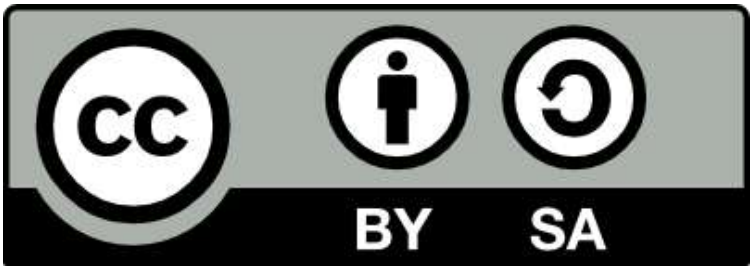

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Abstract

Fluid resuscitation is a commonly used treatment that has the potential to be life-saving when used correctly but harmful in excess. This is particularly true in sepsis where harm has been described in the absence of clinical features of hypervolaemia. Despite this, it is unclear how patients with sepsis should be assessed for fluid resuscitation in an acute medical setting. Furthermore, clinicians frequently fail to perform a fluid assessment, raising questions about the underlying decision-making process.

A systematic review of diagnostic test accuracy studies was completed to assess diagnostic tests that identify a need for fluid resuscitation as defined by the presence of fluid responsiveness. It identified 14 studies in adults with sepsis who would be appropriate for admission to an acute medical unit. Five categories of index test were studied (haemodynamic change following passive leg raise, haemodynamic change with respiration, haemodynamic change following fluid bolus, inferior vena cava collapsibility index and static assessment tools), however a high level of heterogeneity and a high risk of bias prevented meaningful comparisons.

A qualitative study was then undertaken to explore the decision-making process used by acute physicians to determine when fluid resuscitation was required. 18 clinicians of varying grades consented to a semi-structured interview. Transcripts were coded and analysed using thematic analysis. The decision-making process was heavily influenced by the identification of a patient as sick, which was informed by a limited fluid assessment, as well as a ‘pro-fluid’ culture that limited the impact of features of fluid overload. More experienced clinicians valued a flexible approach to

decision-making in contrast to junior clinicians who preferred a standardised approach. Both decision-making approaches were informed by information from the limited assessment. Clinicians of all grades also highlighted a ‘proper’ assessment, based on learning at medical school, which was felt to be important yet simultaneously ineffective.

Because of the dearth of evidence identified by the systematic review, the guideline development group of NICE CG174 has had to rely on consensus opinion to develop recommendations on how the decision to give fluid resuscitation should be made. Of note, their recommendations matched the findings of the qualitative study. To address this evidence gap, the effectiveness of commonly used diagnostic tests, such as fluid responsiveness, should be evaluated. In addition, the decision-making process that clinicians use to determine when fluid responsiveness is required should be explored so that future iterations of guidelines can reflect current clinical practice.

Acknowledgements

This thesis represents the culmination of several years' work and would not have been possible without the input of so many key individuals.

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1 Introduction

Intravenous (IV) fluid is a critical and commonly-used hospital treatment. Despite its low cost (one litre of 0.9% saline costs £2.33[1]), the NHS spends more than £156 million on its use every year[2]. It can be prescribed for three broad indications: fluid resuscitation, fluid and electrolyte replacement and fluid maintenance.

Fluid resuscitation describes the rapid administration of IV fluid to restore a patient's circulating blood volume and increase venous return to the heart. It is a commonly-used treatment for shock, defined as an acute circulatory failure leading to inadequate oxygen delivery to the cells[3]. However, its evidence base is variable. In some scenarios, such as traumatic blood loss, there is good evidence to support its use[4,5]. In acute medicine, however, the evidence base is less established. While it is regarded as "…an essential part of the treatment of any form of shock"[6, p. 1727], no randomised-controlled trial or cohort study supports its use for any acute medical presentation.

Despite this, strong recommendations for the use of fluid resuscitation are found in many medical guidelines. For example, the British Society of Gastroenterology (BSG) care bundle for the early management of acute upper gastrointestinal (GI) bleeding[7] strongly recommends fluid resuscitation for all patients with an acute upper GI bleed while simultaneously noting the evidence to support this recommendation is very low. However, this recommendation can be justified by the widespread belief that for patients with shock, prompt fluid resuscitation is lifesaving[8]. While there is

currently no evidence to support its use in acute medicine, fluid resuscitation is a commonly used treatment and "a cornerstone of modern therapy"[9, p. 503].

1.1 Assessment for Fluid Resuscitation

To determine when IV fluid is required, clinicians are trained to perform a fluid assessment. If hypovolaemia is identified, then urgent fluid administration is advised. If hypervolaemia is noted, then IV fluid should be stopped. The clinical signs that identify hypovolaemia and hypervolaemia are well described in medical textbooks and the literature[10]. However, none are specific to a patient's volume status[11] and many are challenging to assess in the acute setting[12]. A recent systematic review of 30 studies[13] presented data on the relationship between clinical signs of hypovolaemia and blood loss. It found a limited association between the two. When a Receiver Operating Characteristics Curve (ROCC) was used to determine the accuracy of commonly used clinical signs in predicting blood loss, the Area Under the Curve (AUROC) ranged between 0.56 and 0.74 for heart rate and 0.56 and 0.79 for blood pressure. The same issue is true of hypervolaemia. Its clinical features can signify many other medical conditions[11].

The recognition of hyper- and hypovolaemia is therefore challenging and acknowledged as such in the literature[14]. This complexity is increased because of the many patient and disease variables that affect a patient's fluid balance (*Figure 1*). A patient's maximal cardiac output[15] and heart rate response to stressors[16] decline with age. Comorbidities can augment these changes. Heart failure, for example, leads to inappropriate activation of the renin-angiotensin system and an expansion of the extracellular fluid volume[17]. Medications also alter fluid balance,

through direct action via adverse effects such as diarrhoea, or through indirect means, such as the xerostomia caused by anticholinergic medications[18].

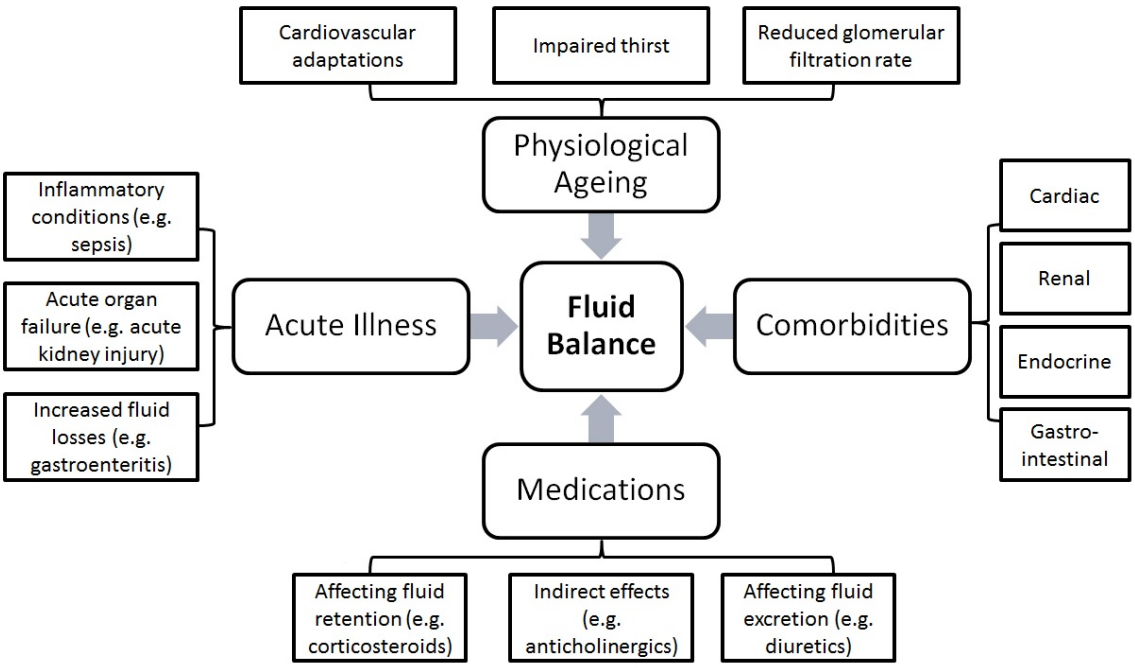

Figure 1.1: Factors that can impact a fluid assessment. Four categories are described which affect fluid balance and therefore a clinician's approach to assessment. Adapted from Seccombe and Sapey[14].

Acute illness adds a further level of complexity. In sepsis, for example, fluid resuscitation can be harmful even in the absence of hypervolaemia. The FEAST (Fluid Expansion As Supportive Therapy) trial[19] took place in Eastern Africa and randomised children (aged 60 days to 12 years) with a severe febrile illness and evidence of impaired perfusion to receive a fluid bolus of 5% albumin, a fluid bolus of 0.9% saline or no fluid bolus. The baseline characteristics (including demographic data, cause of illness and severity of shock) were similar across all groups. While the trial aimed to determine whether 5% albumin or 0.9% saline was a better treatment, it found that fluid boluses increased mortality compared to no fluid bolus. Further

analysis of the mortality at 48 hours (using blinded clinical narratives and pre-specified criteria to determine the cause of death) suggested that the majority of deaths were not due to pulmonary oedema but occurred due to cardiovascular collapse[20]. Yet, according to current teaching, the symptoms and signs of cardiovascular collapse are associated with a diagnosis of hypovolaemia and support the administration of additional fluid boluses[11]. However, the study population (children with a high prevalence of malaria and anaemia in a setting without easy access to mechanical ventilation) is markedly different from that seen in a UK acute medical setting. To date, no equivalent randomised-controlled trials have yet been completed in Europe or in adult populations.

Despite this and the aforementioned complexity, clinicians frequently prescribe IV fluid without a documented fluid assessment. A recent audit of 619 patients presenting with acute kidney injury (AKI) performed across 14 hospital sites in the West Midlands[21] found that 45.7% of patients had no documented evidence of a fluid assessment in their medical records. This was despite the audit accepting any mention of fluid balance in the medical records, including descriptive text such as ‘dehydrated’ or ‘hypovolaemic’. While this could be explained by a general lack of documentation, all of these patients had documented evidence of a respiratory and abdominal examination. Of this 45.7%, 99.5% were given IV fluid. Because of the limited documentation, it is unclear whether these fluid doses were justified and it is also unclear how the decision to prescribe fluid was made. Currently, no evidence exists to explain the decision-making process behind the prescription of fluid resuscitation in any setting.

1.2 Recommendations from Guidelines

For the majority of diseases, national and international guidelines have not specified a dedicated approach for the assessment and administration of fluid. One exception is sepsis. In the last decade, two major guidelines have been published that aim to address the uncertainty surrounding the assessment and prescription of IV fluid. Each approached this challenge in two different ways. The Surviving Sepsis Campaign (SSC)[9] advised a protocolised approach to fluid administration in sepsis. In place of a fluid assessment, they recommended an empirical, fixed dose of IV fluid once septic shock was diagnosed: 30 ml/kg within three hours. This recommendation was based on the results of a single-centre, non-blinded trial of early goal-directed therapy (EGDT) in 263 patients with sepsis[22]. The study noted a 16% mortality reduction when EGDT was used in place of usual care. But, three subsequent trials, which recruited a combined total of 4,175 patients, were unable to replicate these results[23-25]. In addition, a retrospective cohort study found that following EGDT recommendations led 67% of patients to show evidence of fluid overload at 24 hours with a corresponding 92% increased risk of mortality[26].

The latest National Institute for Health and Care Excellence (NICE) guideline for the recognition, diagnosis and early management of sepsis[27] advises that the 2013 NICE clinical guidelines 174 (CG174) for IV fluid use in adults[28] should be followed to determine when fluid resuscitation is indicated. *Figure 2* summarises their recommended assessment strategy. An initial ABCDE assessment is suggested to identify hypovolaemic patients. If hypovolaemia is not identified, then an assessment strategy akin to that found in medical curricula is advised, i.e. one that uses

information taken from a patient's "history, clinical examination, current medications, clinical monitoring and laboratory investigations"[28, p. 8].

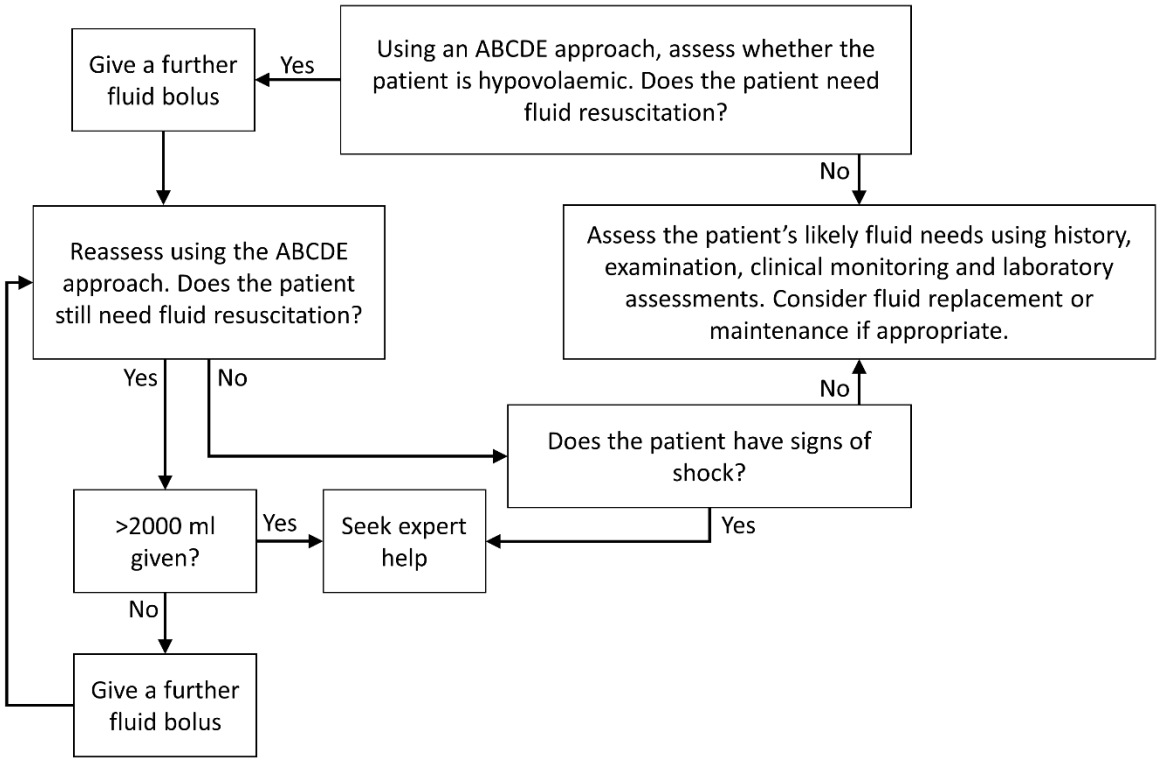

Figure 1.2: The NICE CG174 Assessment and Fluid Resuscitation Algorithm. An ABCDE assessment to advised to identify a need for fluid resuscitation. If fluid resuscitation is not required, a broader fluid assessment is subsequently advised to identify a need for fluid replacement and maintenance[28].

The guidelines go on to describe six criteria that should be used to identify hypovolaemia (see *Table 1*). However, the diagnostic ability of these criteria is open to question. Hypotension and tachycardia are non-specific markers of all forms of shock, including those in which fluid resuscitation may be harmful. The National Early Warning Score (NEWS) identifies acutely unwell patients rather than those who need IV fluid. The same is true of tachypnoea. The evidence base for the use of capillary refill time (CRT) in adults is limited. Moreover, one study noted that the 95%

confidence limit for a normal CRT in older adults (aged over 62 years) extends to 4.5 seconds[29], suggesting the recommended cut-off would not be sensitive in this demographic.

Parameter	**Indicator of hypovolaemia**
Systolic blood pressure	<100 mmHg
Heart rate	>90 beats/min
Capillary refill time	>2 s
Respiratory rate	>20 breaths/min
National Early Warning Score	>4
Urine output	Not mentioned
Passive leg raise	Fluid responsiveness demonstrated

Table 1.1: NICE recommended parameters to diagnose hypovolaemia. This table summarises the clinical criteria for the diagnosis of hypovolaemia that are listed in different sections of the NICE CG174[28].

Fluid responsiveness, as demonstrated by a passive leg raise (PLR), is the sixth criterion and is also recommended by the SSC guidelines[9]. A PLR causes a transient transfer of blood from the legs to the torso[30]. If this increase in preload causes an improvement in the patient's haemodynamic function, the patient is said to be fluid responsive. The concept is based on the Frank-Starling curve[31] (*Figure 3*). In addition to a PLR, the presence of fluid responsiveness can also be assessed by observing the haemodynamic response to a fluid bolus or by measuring the haemodynamic variation during respiration[32]. Tests that identify fluid responsiveness

are known as dynamic assessment tools as they describe a change between two or more measurements. They are in contrast to static assessment tools (e.g. central venous pressure) that aim to diagnose hypovolaemia based on a single measurement.

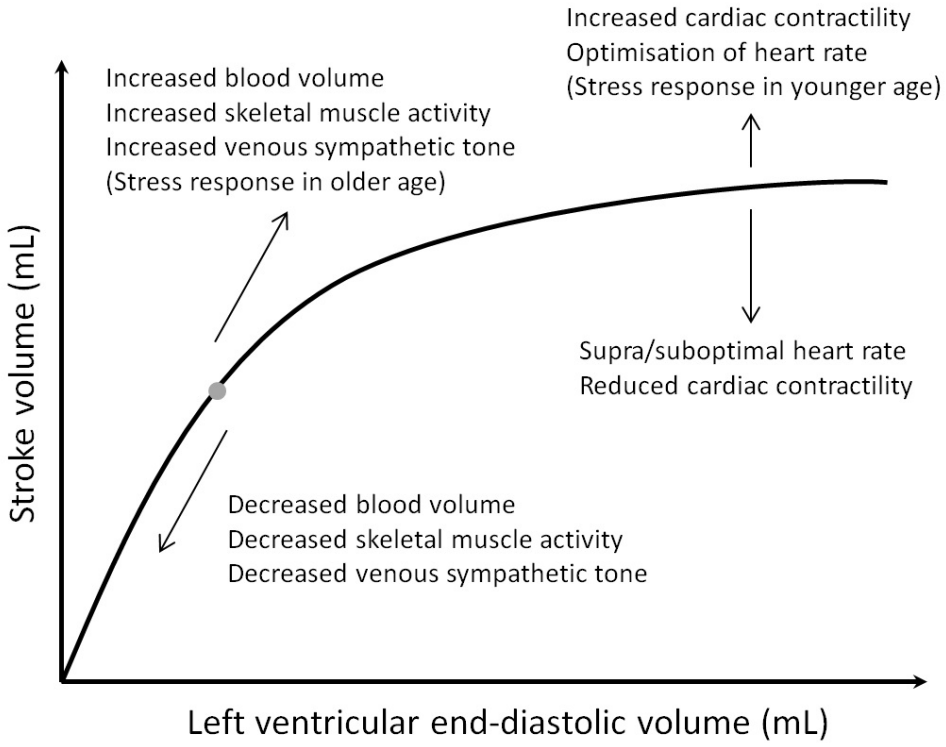

Figure 1.3: The Frank-Starling Curve. The Frank-Starling curve describes the effects of increasing preload on the stroke volume. Factors can alter this relationship by affecting the preload (diagonal arrows) or by altering cardiac function directly (vertical arrows). Adapted from Seccombe and Sapey[14].

1.3 Aims

In summary, fluid resuscitation is a common and important therapeutic intervention that has the potential to cause harm as well as benefit. Ensuring it is given to the right patients is, therefore, essential. Despite this, clinicians frequently prescribe IV

fluid without documenting evidence of a fluid assessment, raising questions about how the decision to prescribe fluid resuscitation is being made.

In addition, guidelines for sepsis recommend the use of assessment tools that either have no evidence base outside of ICU or are not accurate markers of hypovolaemia. One assessment tool that has the potential to be a specific and sensitive part of the assessment process is the PLR. Incorporating it into an assessment for fluid resuscitation could improve patient outcomes, particularly in sepsis where fluid resuscitation can be harmful even in the absence of hypervolaemia. However, the evidence base to support its use in an acute medical setting is currently unclear.

In summary, this thesis tested the hypothesis that there is limited evidence to support the assessment of fluid resuscitation in an acute medical setting and that, as a result, clinicians use individualised decision-making processes that arise from clinical experience and the culture in which they work.

This thesis has two aims:

1. To summarise the evidence base for fluid resuscitation assessment tools in adults patients with sepsis who would be appropriate for admission to the acute medical unit, particularly those that identify fluid responsiveness.
2. To explore the decision-making process used by acute physicians for fluid resuscitation in the acute medical setting.

2 A Systematic Review of Diagnostic Test Accuracy Studies Exploring the Assessment for Fluid Resuscitation in Awake, Septic Adults

This systematic review has been published as Seccombe A, McCluskey L, Moorey H, Lasserson D, Sapey E. Assessing Fluid Resuscitation in Adults with Sepsis Who Are Not Mechanically Ventilated: a Systematic Review of Diagnostic Test Accuracy Studies. J Gen Intern Med. 2019 Sep;34(9): 1874-1883.

2.1 Introduction

Over the last two decades, studies and systematic reviews[33-36] have explored the ability of fluid assessment tools to predict fluid responsiveness in critically unwell patients with sepsis. However, each of these studies was based in ICU, using patients who are sedated and ventilated. Because differences in accuracy between mechanically-ventilated and non-mechanically-ventilated patients have been observed[37], these findings may not translate to acute medical patients. To date, no systematic reviews have explored the evidence base for fluid responsiveness in an acute medical setting.

This systematic review tested the hypothesis that the PLR is the most accurate diagnostic test that is appropriate to perform in an acute medical setting to predict the presence of fluid responsiveness in adults patients with sepsis.

To address this hypothesis, the following review questions were developed:

1. What approaches are described in the literature to assess a need for fluid resuscitation in awake patients who are admitted to hospital with a diagnosis of sepsis?
2. What is the diagnostic accuracy of these approaches?

2.2 Method

The reporting of this systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines[38]. A protocol was completed and published on PROSPERO before commencing the systematic review (CRD42017048651)[39].

2.2.1 Search strategy

Search strategies were created for the following bibliographic databases: Medline (Ovid) from 1946; Embase (Ovid) from 1947; CINAHL (Ebsco) from 1937; and the Cochrane Library (Wiley) from 1996.

An electronic database search was undertaken using a combination of keywords and subject headings encompassing three domains: sepsis, intravenous fluid, and patient location. No restrictions on publication language or date were applied. The search strategies were piloted before use. *Appendix 1* contains the search strategy used for Medline. Before the completion of the review, the searches were repeated to ensure inclusion of the latest literature.

To reduce the risk of publication bias, the following supplemental searches were performed: hand-searching of the references of included articles and relevant

systematic reviews, forward-citation searching of included articles using Web of Science, searching the Zetoc database (The British Library) and the Conference Proceedings Citation Index (Web of Science) for grey literature, and searching three research registers (ClinicalTrials.gov, the UK Clinical Research Network Study Portfolio Database, and the World Health Organization International Clinical Trials Registry Platform) to identify relevant, ongoing studies.

The results from the above searches were entered into reference management software [Endnote version 7.3.1 (Clarivate Analytics, Philadelphia, PA, USA)]. Duplicate records were removed using an automated algorithm and then by manual searching.

2.2.2 Study selection

Studies were considered for inclusion based on the eligibility criteria summarised in *Table 2*. The review included all diagnostic test accuracy studies that compared one or more index test with a reference standard that identified a need for fluid resuscitation in adult (aged >18 years) participants who had been admitted to hospital, including those in the emergency department (ED).

Because initial scoping found few studies, the inclusion criteria were not limited to specific types of diagnostic test accuracy study (i.e. both single-gate and two-gate methodologies were accepted). The definition of sepsis was also broadened to sepsis as defined by any previous international consensus definition[40-42] or the presence of a confirmed infection. If a study included multiple diagnoses, they were

included if individual patient data was obtained or if greater than 50% of participants had sepsis or confirmed infection.

During scoping, it was also noted that most studies were based in ICU. Because the proportion of patients who were sedated or anaesthetised was rarely reported, it was decided that studies set in ICU could be included if they did not include patients who were mechanically ventilated. Studies that included pregnant women, burns patients, trauma patients or perioperative patients were excluded.

Study Design	Diagnostic test accuracy studies
Participants	Adults (aged ≥18 years) with sepsis of any severity or confirmed infection. Studies were excluded if they involved children, pregnant women, burns patients, trauma patients, perioperative patients, or patients who were mechanically ventilated.
Index Test	Any history question, examination technique, or diagnostic test
Reference Standard	Any
Target Condition	Hypovolaemia or a need for fluid resuscitation

Table 2.1: Study Selection Criteria. This table summarises the pre-defined study selection criteria.

An initial screening of titles and abstracts was completed independently by two reviewers using the above criteria. The full manuscripts of selected studies were then reviewed. Disagreements were resolved through discussion and, if necessary, a

third reviewer. All results were tabulated using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

2.2.3 Data extraction

Data were extracted using a piloted, standardised form after translation of non-English language articles if required. The following data were extracted: study characteristics (including setting and sample size); patient characteristics (including age, gender, acuity score, blood pressure, heart rate, the preceding volume of IV fluid administered, concurrent use of vasopressors/inotropes, and admission diagnoses); and details of the index test(s), the reference standard, and the target condition.

2.2.4 Evidence synthesis

Data extracted from each study were tabulated and incorporated into a qualitative narrative analysis to provide a descriptive synthesis. While the protocol detailed strategies for the assessment of heterogeneity (through visual inspection and, statistical analysis), for meta-analyses and for sub-group analyses, there was a high degree of heterogeneity between included studies. As a result, any quantitative analyses would have been susceptible to bias and clinically unhelpful. Separate pooling of sensitivity and specificity estimates in forest plots was considered but excluded as this approach fails to account for trade-offs between sensitivity and specificity and can lead to underestimates of test accuracy[43]. The risk of bias and study quality were assessed using the QUADAS-2 quality assessment tool[44] as advised by the Cochrane Handbook of Diagnostic Studies[45].

2.3 Results

2.3.1 Summary of searches

Searches of the four bibliographic databases (Medline, Cochrane, EMBASE and CINAHL) returned a total of 26,481 records. An additional 216 records were identified from the conference proceedings databases and trial registries. Following initial screening, 463 full-text articles were reviewed for eligibility. 12 studies were identified for inclusion and 2 additional articles were identified from the references of included articles[46-59]. *Figure 4* summarises the selection process and details the reasons for exclusion.

2.3.2 Study characteristics

The median sample size of the 14 included studies was 33 (range 14-116). Three were published only as a conference abstract. 12 were set in ICU and two were set in ED.

Nine studies based their inclusion criteria around a composite definition of shock, (most commonly named ‘acute circulatory failure’) which was defined by a heterogeneous combination of haemodynamic markers, clinical signs and blood tests. Blood pressure was the most common single reason for study inclusion. In 13 studies, patients met the inclusion criteria if they were hypotensive alone (*Table 3*). The most common reason for exclusion was arrhythmia, which included atrial fibrillation and was present as an exclusion criterion in seven studies. One study excluded all patients with any form of cardiac disease.

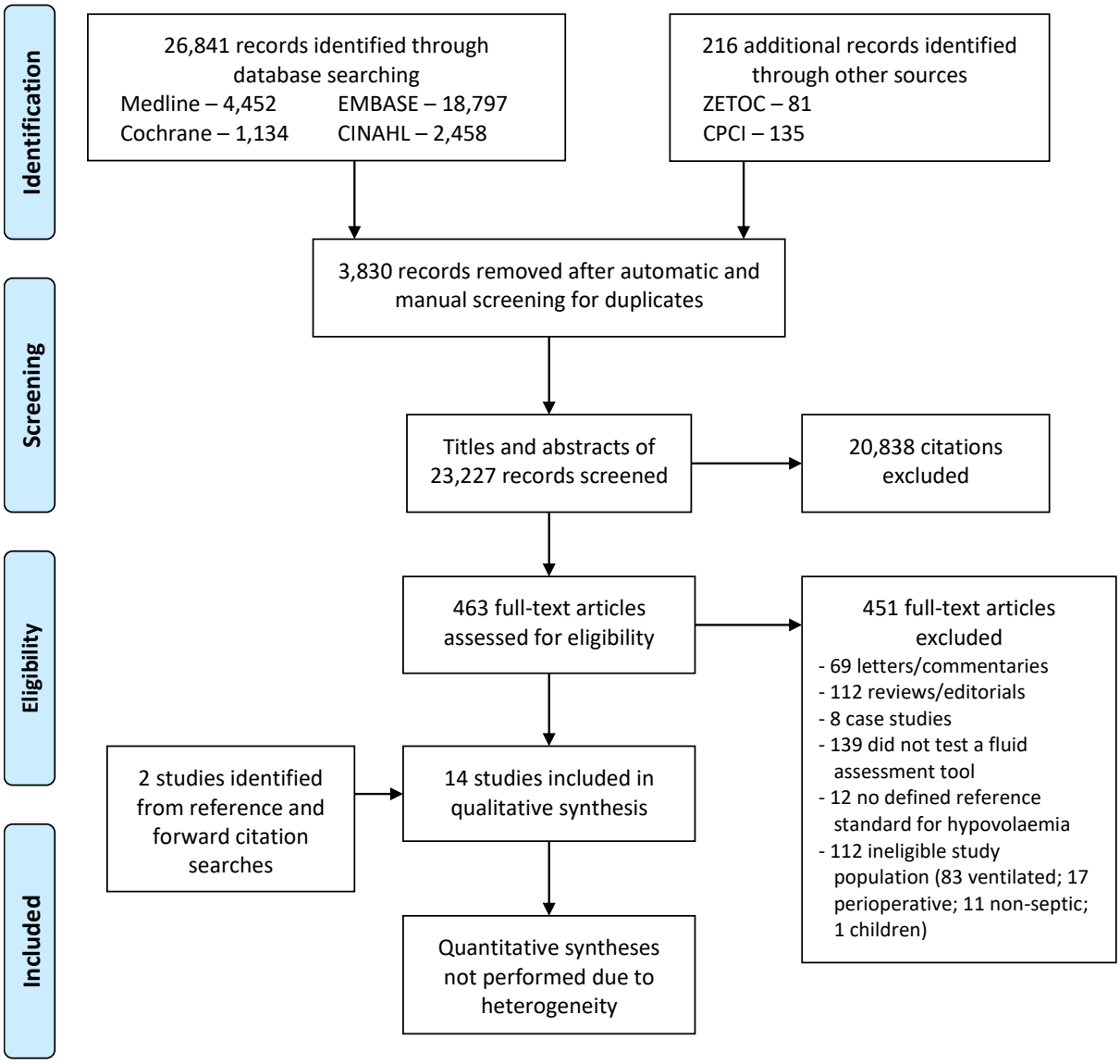

Figure 2.1: PRISMA diagram summarising the study selection process. The number of studies reviewed at all stages of the study selection process is documented including the reasons for exclusion of all full-text articles that were reviewed.

2.3.3 Patient population

Eight studies only included patients with sepsis. Individual patient data for patients with sepsis was received from an additional two studies. Four studies did not respond to requests for additional data but were included as greater than 50% of patients were diagnosed with sepsis or confirmed infection. Of note, patients with an admission diagnosis of congestive cardiac failure were included in two of these studies.

The recording of preceding IV fluid use was mentioned in only five studies. In two of these, patients received a median of 4L prior to participation, approximately double the 30ml/kg initial fluid resuscitation dose recommended by the SSC guidelines[9] (see *Table 4*).

2.3.4 Target condition

Fluid responsiveness was the target condition in all studies. However, the justification to use it as a proxy for hypovolaemia was not articulated in any study. In fact, nine studies did not use the term 'hypovolaemia' at any point in the published manuscript (see *Table 3*).

2.3.5 Reference standard

There was significant heterogeneity in the tests used to determine the presence or absence of fluid responsiveness, i.e. the reference standard (see *Table 5*), and only two studies, which shared the same first author, had the same definition of fluid responsiveness[54,56]. There was also a marked variation in the percentage of patients

meeting the reference standard: median 50% (range 17.4%-65.4%) between the included studies.

Two studies used static tests to identify fluid responsiveness, both of which were recommended by the Surviving Sepsis guidelines[9]. The remaining 12 studies used a dynamic test. 11 of these studies identified fluid responsiveness using a rise in cardiac function. The most common measurements used were cardiac index (4 studies) and stroke volume (4 studies). The most common measurement tool was echocardiography (8 studies). One study used an absolute (>10mmHg) rise in non-invasive systolic blood pressure following a fluid bolus.

All of the 12 studies that used a dynamic test to identify fluid responsiveness used a fluid bolus as part of the reference standard. Nine studies administered a fixed 500mL bolus. The other three studies administered a weight-based bolus which ranged between 490 and 2,100mL for a 70kg patient. The rate at which the bolus was given ranged between 15-30 minutes, except in one study where the infusion rate was noted to be variable. Five studies used a crystalloid fluid, six used a colloid and one did not specify which type of fluid was used.

2.3.6 Index tests

Five different categories of diagnostic test were evaluated by the included studies (see *Table 6*): inferior vena cava (IVC) measurements, change with respiration, change following IV fluid, change with passive leg raise (PLR) and static measurements.

Six studies assessed the inferior vena cava collapsibility index (IVCCI), calculated by dividing the difference in IVC diameter during respiration by the end-expiratory IVC diameter. Four of these studies tested the diagnostic accuracy of IVCCI before a fluid bolus was given against the response of a measure of left-ventricular function to a fluid bolus as a marker of fluid responsiveness. The AUROC for IVCCI was comparable for each of these studies (0.77, 0.82, 0.82, 0.83). A fifth used systolic blood pressure to identify fluid responsiveness, giving an AUROC of 0.68. The final study looked at IVCCI after a fluid bolus was given and reported an AUROC of 0.91.

Three studies explored haemodynamic change after a PLR, although two of these were published as a conference abstract only. A further three studies reported haemodynamic change during respiration. Finally, two studies explored a static tool as part of their primary aim and one study assessed haemodynamic change after a fluid bolus, the reference standard in twelve of the other included studies.

2.3.7 Risk of bias assessment

Several factors contributed to a high overall risk of bias (see *Figure 5*). Firstly, the reference standards were heterogeneous and unjustified. Two studies acknowledged their chosen reference standard (central venous pressure[57] and blood pressure/lactate levels[58]) would not effectively identify fluid responsiveness because it was a static test. This would bias estimates of sensitivity and specificity, assuming that fluid responsiveness is equivalent to hypovolaemia. The remaining 12 studies used fluid responsiveness, however, none provided satisfactory evidence to support their choice of reference standard.

Secondly, 12 studies did not report acceptable observer variation data: one described intra-observer variation only, one described the observer variation of a healthy cohort, one described inter-observer variation that was greater than the index test's threshold values (making the cut-off invalid) and nine provided no data.

Thirdly, only five of the studies reported the percentage of tests results that were inconclusive or uninterpretable: three for echocardiography (11.5%, 12.8% and 16.1%); two for IVCCI (12.5%, 13.5%).

Finally, 12 studies calculated the index test's optimal threshold using *post-hoc* analysis, i.e. there was no *a priori* definition of a diagnostic cut-off. This is likely to explain why, in the six studies that assessed IVCCI, the thresholds varied between >15% to >50% (median >37%).

Author	Year	Setting	No. of patients	Patient Population	Primary Index Test(s)	Additional Index Test(s)	Reference standard	Target Condition	Hypovolaemia mentioned?
de Valk[46]	2014	ED, Netherlands	23*	Shock (SBP<90, SBP >40 less than normal, HR >100, CRT >2s or Lactate >2)	IVCCI	None	Rise in SBP after fluid bolus	Fluid responsiveness	Yes
Corl[47]	2017	ED/ICU, USA	55*	ACF (SBP<90/MAP<65 for >30 mins, UO<0.5, HR>120 for >30 mins, pH<7.3 or lactate >2)	IVCCI	Change in IVCCI after fluid and PLR, IVCDi/e	Rise in CI after fluid bolus	Fluid responsiveness	No
Muller[48]	2012	ICU, France	40	ACF (MAP<65, UO<0.5, tachycardia, mottled skin or lactate >2)	IVCCI	E wave velocity, LVOT VTI, E/A ratio, E/Ea ratio	Rise in LVOT VTI after	Fluid responsiveness	No
Preau[49]	2017	ICU, France	90	Sepsis and ACF (SBP <90, SBP >40 less than normal, UO <0.5, HR>100 or mottled skin)	IVCCI ± standardised respiration	IVCD, SVI	Rise in SVI after fluid bolus	Fluid responsiveness	Yes
Lanspa[50]	2013	ED/ICU, USA	14	Sepsis and refractory hypotension (SBP<90 after >20ml/kg of IV fluid)	IVVCI, AoVV and SVV	None	Rise in CI after fluid bolus	Fluid responsiveness	No
Abodorra[51] **(Poster)**	2014	ICU, Egypt	40	Sepsis and ACF (undefined)	IVCCI (after fluid bolus)	Change in IVCCI after fluid	Rise in LVOT VTI after fluid bolus	Fluid responsiveness	No
Dutta[52] **(Poster)**	2014	ED/ICU, India	116	Sepsis and hypotension (undefined)	Change in SV after PLR	None	Rise in SV after fluid bolus	Fluid responsiveness	Yes
Klarer[53] **(Poster)**	2010	ICU, Switzerland	27	Hypotension (MAP<60 mmHg) and/or reduced CI (CI <2.7 L/min/m2)	Change in CI, SVI, and MAP after PLR	None	Rise in CI after fluid bolus	Fluid responsiveness	No

Author	Year	Setting	No. of patients	Patient Population	Primary Index Test(s)	Additional Index Test(s)	Reference standard	Target Condition	Hypovolaemia mentioned?
Preau[54]	2010	ICU, France	34	Sepsis or acute pancreatitis and ACF (SBP <90, SBP >40 less than normal, UO <0.5, HR>100 or mottled skin)	Change in SV, PP, and VF after PLR	None	Rise in SV after fluid bolus	Fluid responsiveness	Yes
Soubrier[55]	2007	ICU, France	32	Haemodynamic instability (SBP<90, MAP <75, SBP >40 less than normal, UO <0.5 over 3 hours, HR >100 or mottled skin)	PPV and SBPV ± standardised respiration	None	Rise in CI after fluid bolus	Fluid responsiveness	Yes
Preau[56]	2012	ICU, France	23	ACF (SBP <90, SBP >40 less than normal, UO <0.5 for >1 hour, HR>100 or mottled skin)	PPV and VFV ± standardised respiration	None	Rise in SV after fluid bolus	Fluid responsiveness	No
Jung[57]	2012	ED, South Korea	26	Sepsis and hypotension (SBP <90, MAP <70, SBP >40 less than normal in the absence of another cause)	FTc	CVP, IVCD	Rise in SV after fluid bolus	Fluid responsiveness	No
Keller[58]	2009	ICU, USA	44	Any admission to ICU with a plan to insert a CVC	IJV aspect ratio	None	CVP < 8mmHg	Fluid responsiveness	No
Soliman[59]	2017	ICU, Egypt	30	Sepsis and hypotension (MAP<65) or impaired tissue perfusion (lactate >4)	Change in CO after fluid	None	MAP >65 and lactate <4	Fluid responsiveness	No

Table 2.2: Main Characteristics of Included Studies. This table summarises the 14 included studies. * = individual patient data provided by the authors. The primary index tests were those mentioned in the study's aim. ACF: Acute circulatory failure, AoVV:

Aortic velocity variation, CI: Cardiac index, CO: Cardiac output, CRT: Capillary refill time, CVP: Central venous pressure, ED: Emergency Department, FTc: Corrected flow time, HR: Heart rate, ICU: Intensive Care Unit, IJV: Internal jugular vein, IVCCI: Inferior vena cava collapsibility index, IVCDi/e: End-inspiratory/expiratory inferior vena cava diameter, LVOT VTI: Left ventricular outflow tract velocity time integral, MAP: Mean arterial pressure, PLR: Passive leg raise, PP: Pulse pressure, PPV: Pulse pressure variation, SBP: Systolic blood pressure, SBPV: Systolic blood pressure variation, SV: Stroke volume, SVI: Stroke volume index, SVV: Stroke volume variation, UO: Urine output, VF: Femoral artery velocity, VFV: Femoral artery velocity variation.

Author	Year	Male (%)	Age (years)	MAP (mmHg)	HR (bpm)	Diagnoses	Additional treatment	Preceding IV fluid (L)
de Valk[46]*	2014	23 (47.8)	54.6 ± 18.0	75.3 ± 14.6	117.1 ± 8.0	Sepsis (100)	-	M 100 (Q 0 - 325)
Corl[47]*	2017	23 (41.8)	67.9 ± 18.6	99.3 ± 18.9	114.7 ± 29.5	Sepsis (100)	Vasopressors (58.1)	M 4000 (Q 3350-6000)
Muller[48]	2012	-	M 63 (5P 56, 95P 70)	M 71 (5P 66, 95P 77)	M 101 (5P 91, 95P 116)	Sepsis (60), Bleeding (27.5), Dehydration (12.5)	-	-
Preau[49]	2017	58 (64.4)	55.2 ± 28.9	Unknown	102.1 ± 32.8	Sepsis (100)	Vasopressors (15.6)	(within 24 hours) M 1000 (0-2500)
Lanspa[50]	2013	5 (35.7)	M 62 (Q 46-81)	M 65 (Q 61-70)	M 102 (Q 80-112)	Sepsis (100)	Vasopressors (57)	M 4600 (Q 3000-5900)
Abodorra[51]	2014	-	53.5 ± 14.3	57.5 ± 11.7	107.9 ± 11.5	Sepsis (100)	-	-
Dutta[52]	2014	-	-	Unknown	Unknown	Sepsis (100)	-	-
Klarer[53]	2010	-	M 60 (R 29-82)	M 61 (R 48-104)	M 104 (R 53-145)	Sepsis (51.9), Heart failure (18.5), Respiratory failure (14.8), Other (14.8)	Vasopressors/inotropes (100)	-
Preau[54]	2010	19 (55.9)	53 ± 19	76.9 ± 14.4	100.8 ± 21.5	Sepsis (82.4), Acute pancreatitis (17.6)	Vasopressors (18)	-
Soubrier[55]	2007	9 (28.1)	61 ± 13	89 ± 14	103 ± 16	Sepsis (12.5), Pneumonia (75), Haematological disease (3.1), Trauma (6.3), Abdominal surgery (3.1)	Vasopressors (9.4)	25% received IV fluid in preceding 24 hours
Preau[56]	2012	16 (69.6)	50 ± 5	79.4 ± 11.1	103.5 ± 19.1	Sepsis (87.0), Acute pancreatitis (13.0)	-	-
Jung[57]	2012	17 (65.4)	M 73.7 (Q 58-83)	M 56.5 (Q 49.5-65.6)	94 (83-114)	Sepsis (100)	No	-
Keller[58]	2009	22 (50.0)	66 ± 14	67 ± 12	92 ± 22	Sepsis (45.5), GI bleed (13.6), Heart failure (9.1), Not recorded (31.8)	-	-
Soliman[59]	2017	43.3	47.8 ± 19.7	52.9 ± 7.9	-	Sepsis (100)	Vasopressors (not recorded)	-

Table 2.3: Main Patient Characteristics. This table summarises the patient characteristics for the 14 included studies. * = individual patient data. - = data not available. Data are presented as mean ± SD or as median (indicated by 'M') and a measure of spread in brackets ('Q' = quartiles, 'R' = range, and '5P' or '95P' = 5^{th} and 95^{th} percentiles, respectively). Number of patients, names of diagnoses and use of vasopressors are presented with percentages in brackets.

Author	Year	Met Reference Standard (%)	Measurement			Fluid Bolus		
			Parameter	Threshold rise (%)	Measurement tool	Volume	Fluid Type	Rate (mins)
de Valk[46]	2014	17.4	Systolic blood pressure	>10mmHg	NIBP	500mL	0.9% Saline	15
Corl[47]	2017	56.4	Cardiac index	>10	Bioreactance	500mL	0.9% Saline	Pressure bag
Muller[48]	2012	50	LVOT VTI	>15	Echocardiography	500mL	6% Starch	15
Preau[49]	2017	55.6	Stroke volume index	>10	Echocardiography	500mL	4% Gelatin	30
Lanspa[50]	2013	35.7	Cardiac index	>15	Echocardiography	10mL/kg	Crystalloid	<20
Abodorra[51]	2014	50	LVOT VTI	>15	Echocardiography	500mL	Not recorded	15
Dutta[52]	2014	62.9	Stroke volume	>10	Echocardiography	30mL/kg	Crystalloid	Not recorded
Klarer[53]	2010	Not recorded	Cardiac index	>15	Pulse contour analysis	500mL	0.9% Saline	15
Preau[54]	2010	41.1	Stroke volume	>15	Echocardiography	500mL	6% Starch	30
Soubrier[55]	2007	59.4	Cardiac index	>15	Echocardiography	500mL	6% Starch	20
Preau[56]	2012	43.5	Stroke volume	>15	Echocardiography	500mL	6% Starch	30
Jung[57]	2012	65.4	Stroke volume	>10	Oesophageal doppler	7mL/kg	6% Starch	30
Keller[58]	2009	59.1	Central venous pressure <8mmHg via central venous catheter			N/A - static test		
Soliman[59]	2017	33.3	MAP <65mmHg or lactate <4mmol/L (measurement tool unclear)			N/A - static test		

Table 2.4: Summary of Reference Standards. This table summarises the reference standards used by the 14 included studies, including the method of measuring the physiological parameter, whether a dynamic assessment tool was used and the means by which the fluid bolus was given. LVOT VTI: Left ventricular outflow tract velocity time integral, NIBP: Non-invasive blood pressure.

Category of Index Test	Author	Year	Primary Index Tests (Measurement tool)	Threshold	AUROC	Sn	Sp	PPV	NPV
Inferior Vena Cava	de Valk[46]*	2014	IVCCI (US)	≥36.5%	0.68 (0.37-0.98)	75	57.9	27.3	97.7
	Corl[47]*	2017	IVCCI (US)	≥25%	0.82 (0.68-0.95)	83.9	79.2	83.9	79.2
	Muller[48]	2012	IVCCI (US)	≥40%	0.77 (0.60-0.88)	70	80	77.8	72.7
	Preau[49]	2017	IVCCI (US)	≥48%	0.82 (0.73-0.91)	76	88	88	75
			IVCCI with standardised respiration (US)	≥31%	0.89 (0.82-0.97)	84	90	91	82
	Lanspa[50]	2013	IVCCI (US)	≥15%	0.83 (0.58-1.00)	100	67	62	100
	Abodorra[51]	2014	IVCCI after 100mL (US)	>45%	0.91	90	65	72	88.7
PLR	Dutta[52]	2014	Change in SV (Echo)	≥15%	-	87.7	100	100	82.7
	Klarer[53]	2010	Change in CI (PC)	>15%	-	-	-	50	86
			Change in SVI (PC)	>15%	-	-	-	20	77
			Change in MAP (PC)	>10%	-	-	-	12	80
	Preau[54]	2010	Change in SV (Echo)	≥10%	0.94 (0.90-0.98)	86	90	86	90
			Change in PP (PC)	≥9%	0.86 (0.78-0.94)	79	85	79	85
			Change in VF (Echo)	≥8%	0.93 (0.89-0.97)	86	80	75	89
Respiration	Lanspa[51]	2013	AoVV (Echo)	≥25%	0.67 (0.32-1.00)	75	66.7	50	85.7
			SVV (PC)	≥17%	0.92 (0.73-1.00)	60	100	100	81.8
	Soubrier[55]	2007	PPVa (PC)	≥12%	0.81 (0.73-0.89)	63	92	92	63
			SBPV (PC)	≥9%	0.82 (0.74-0.90)	47	92	90	54
			PPVa with standardised respiration (PC)	≥33%	0.72 (0.63-0.81)	21	92	80	44
			SBPV with standardised respiration (PC)	≥30%	0.69 (0.59-0.79)	26	92	80	83
	Preau[56]	2012	PPVa (PC)	≥10%	0.71 (0.59-0.83)	60	100	100	76
			VFV (US)	≥10%	0.74 (0.63-0.85)	60	100	100	76
			PPVa with standardised respiration (PC)	≥12%	0.95 (0.90-1.00)	90	100	100	93
			VFV with standardised respiration (US)	≥12%	0.95 (0.90-1.00)	90	100	100	93
Static	Jung[57]	2012	FTc (Oesophageal doppler)	<301ms	0.87 (0.71-0.98)	88.2	88.8	93.7	79.9
	Keller[58]	2009	IJV aspect ratio (US)	<0.83	0.84 (0.72-0.96)	78	77	83	71
Fluid	Soliman[59]	2017	Change in CO (Bioimpedance) after 30 mL/kg 0.9% saline over 2 hours	>12.5%	0.9	90	70	80	90

Table 2.5: Summary of Studied Index Tests. This table summarises the primary index tests for included studies. * = individual patient data. - = data not available. AoVV: Aortic velocity variation, AUROC: Area under the curve of the Receiver Operating Characteristic, CI: Cardiac index, CO: Cardiac output, FTc: Corrected flow time, IJV: Internal jugular vein, IVCCI: Inferior vena cava collapsibility index, MAP: Mean arterial pressure, NPV: Negative predictive value, PC: Pulse contour analysis, PLR: Passive leg raise, PP: Pulse pressure, PPV: Positive predictive value, PPVa: Pulse pressure variation, SBP: Systolic blood pressure, SBPV: Systolic blood pressure variation, Sn: Sensitivity, Sp: Specificity, SV: Stroke volume, SVI: Stroke volume index, SVV: Stroke volume variation, US: Ultrasound, VF: Femoral artery velocity, VFV: Femoral artery velocity variation.

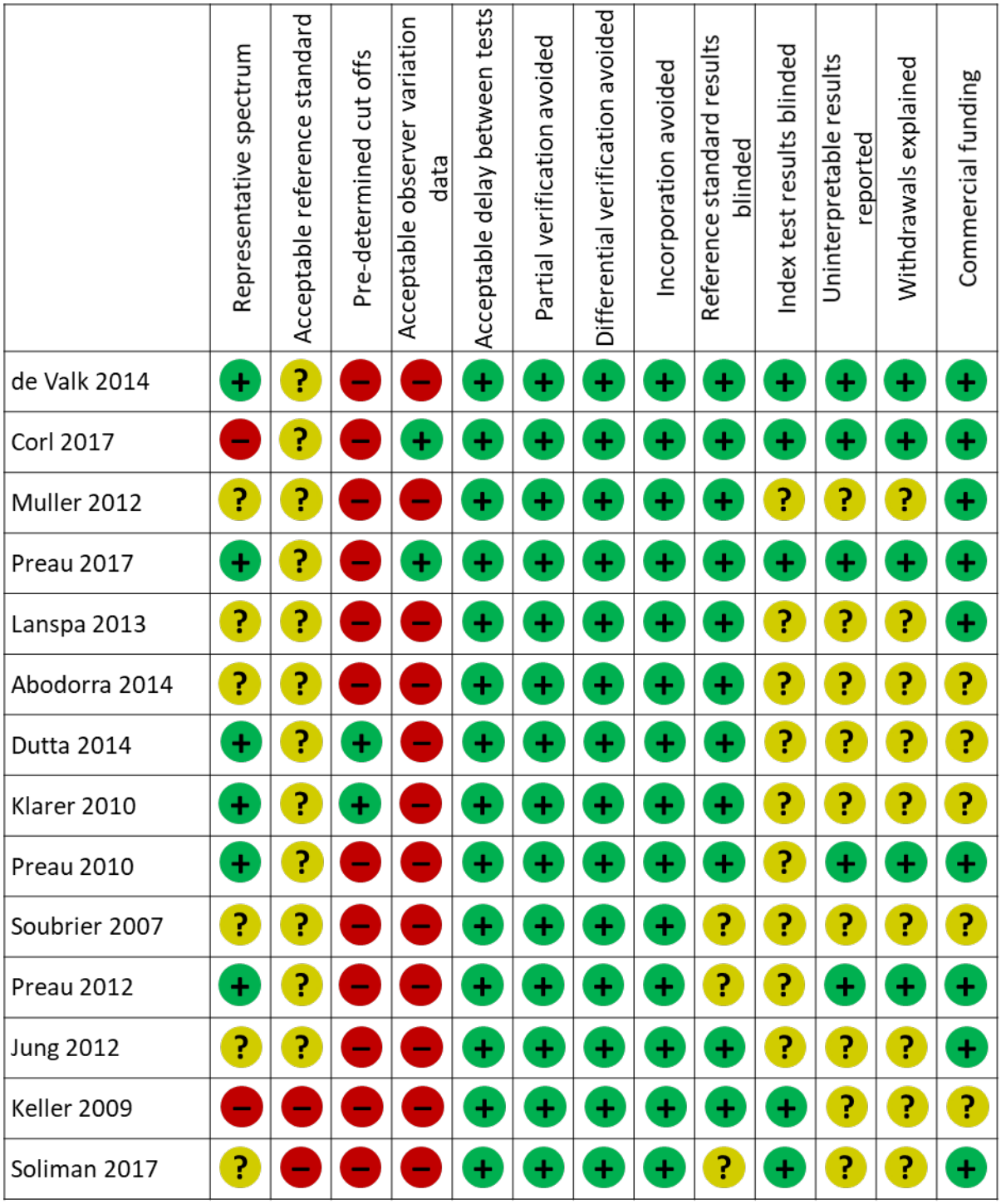

Figure 2.2: Risk of Bias Assessment. This table summarises the risk of bias assessment performed using a modified version of QUADAS-2[45]. + = low risk of bias, ? = unclear risk of bias, - = high risk of bias.

2.4 Discussion

This is the first systematic review that explores diagnostic tests that determine a need for fluid resuscitation in adults with sepsis who are not mechanically ventilated. The review found only a small number of heterogeneous studies available to guide clinical practice. This heterogeneity, and a lack of consensus regarding associated definitions, was consistently noted throughout the literature. As a result, the review was unable to prove or disprove the hypothesis that the PLR manoeuvre is the most accurate diagnostic test that is appropriate to perform in an acute medical setting to predict the presence of fluid responsiveness in adults patients with sepsis.

The heterogeneity between the included studies arose for several reasons. The characteristics of included patients were often poorly described and varied widely between studies. Six studies combined shock due to sepsis with shock arising from other underlying disease processes (e.g. heart failure) and seven studies excluded patients with arrhythmia without justification. The exclusion of such patients reduces the generalisability of the findings given there is a notable prevalence of arrhythmia in older adults (up to 17% of adults >80 years have atrial fibrillation[60]).

Five categories of index test were explored by the included studies. However, even accepting the clinical heterogeneity, the high risk of bias prevented meaningful comparisons. As noted above, 12 studies used index test thresholds that were chosen *post-hoc* and 12 studies did not report adequate observer variability data.

All studies identified fluid responsiveness as the target condition, which was universally seen as synonymous with a benefit from fluid resuscitation. However, the

evidence to support this supposition is not clear. Fluid responsiveness has been observed in healthy volunteers. One observational study found that 45% of volunteers had a greater than 10% rise in stroke volume following a PLR[61]. A second study noted that 58% of volunteers had a greater than 15% rise in cardiac index following a PLR[62]. These results suggest that fluid responsiveness is a physiological finding, i.e. that it occurs in the absence of hypovolaemia. Of note, these results are similar to the median percentage of those with fluid responsiveness in the included studies (50%). This raises questions about whether fluid responsiveness is an effective marker of a benefit from fluid resuscitation.

While no previous studies have attempted to distinguish fluid responsiveness in health from that seen in hypovolaemia, two randomised studies in ED compared a fluid responsiveness protocol to standard care. Neither found a significant benefit for fluid responsiveness based on their primary outcomes (the rate of lactate clearance[63] and change in SOFA score over 72 hours[64], respectively) or the volume of fluid used. However, both studies were small (122 and 64 patients, respectively) and may have been underpowered in a heterogeneous ED population.

Even if fluid responsiveness is assumed to be an effective way of guiding fluid resuscitation and equivalent to hypovolaemia, the absence of a standard definition is limiting clinical practice and further research. Only two studies shared the same definition of fluid responsiveness. Other authors have also noted the heterogeneity in the definition of fluid responsiveness[65] and calls for a consensus definition have been made[66].

With this aim in mind, some authors have suggested that cardiac output is the best means of determining fluid responsiveness[67] as justified by the Frank-Starling curve[31]. However, this recommendation assumes that maximising a patient's cardiac output is always beneficial. There is currently no evidence to support this statement. Furthermore, the ability of an increase in cardiac output to identify a need for fluid resuscitation has never been compared to more commonly used haemodynamic markers, such as blood pressure, nor have the practicalities of monitoring cardiac output on a medical ward been considered by the advocates of such an approach.

2.4.1 Study Limitations

Despite excluding mechanically ventilated patients, the eligibility criteria of this systematic review (see *Table 2*) remained broad. The patients in the included studies were predominantly from an ICU population and many participants had already received significant amounts of IV fluid before study inclusion. This limits the generalisability of the results to an acute medical population. Moreover, focusing on data from critically unwell patients may have artificially increased the sensitivity of the index tests[45]. This risk was noted in the protocol[39] after scoping found a limited evidence base outside of ICU.

The wide clinical heterogeneity meant that statistics to describe the presence of publication bias were not feasible. However, three unpublished conference proceedings were identified by the search strategy. This reflected a robust methodological approach and supports the notion that the low number of included studies was a result of a limited evidence base rather than methodological shortcomings.

A final consideration is the diagnostic test accuracy methodology itself. By dividing the study population into two groups – fluid responsive and fluid non-responsive – this methodology assumes a dichotomous status for each patient. However, as with any biological system, there is a spectrum between being fluid responsive and fluid non-responsive. All of the described index tests provide the clinician with continuous data which would support a nuanced analysis that is appropriate for the complexity seen in our increasing multimorbid patient population. Simplifying these measurement tools, using a cut-off value, limits a clinician's ability to optimise fluid provision.

2.5 Conclusion

Fluid resuscitation is a key recommendation in the guidelines for the management of patients with sepsis[9,28] but evidence to guide an appropriate assessment in the acute medical setting is lacking. There is no consensus definition of hypovolaemia or fluid responsiveness and there is no evidence to support the use of fluid responsiveness as a proxy for hypovolaemia. In addition, there is no consensus on which measurement or measurement tool should be used to identify fluid responsiveness. Finally, once fluid responsiveness has been confirmed, there is no evidence to guide the specifics of treatment, i.e. what volume of which fluid at what rate.

Because fluid resuscitation is a common treatment across all medical specialities, there is an urgent and pressing need for evidence that can address these questions. The prompt administration of fluid resuscitation can be life-saving but, if given in excess, it can lead to patient harm. Further research should, therefore, be a priority.

3 A Thematic Analysis of the Decision-making Behind Fluid Resuscitation

3.1 Introduction

Fluid assessment to determine the presence of hypovolaemia (defined as a significantly reduced intravascular volume) is seen as a key competency within medicine, appearing on curricula for all grades of medical doctor[68-70]. However, no consensus exists on how the decision to give fluid resuscitation should be made. The National Institute for Health and Care Excellence released a set of guidelines in 2013 that made describing fluid assessment a key aim[28] but acknowledged that they were limited by a lack of evidence.

Over the last 189 years[71], doctors have built a wealth of experience in the use of fluid resuscitation but no qualitative studies have attempted to describe how medical doctors of any grade or speciality decide to prescribe fluid resuscitation. Defining normal practice, and when variations from this norm take place, would give future research a baseline from which to work and may identify new processes that could be tested in clinical trials. Because the generated data were analysed inductively and then deductively, no formal hypothesis was developed beyond that already described to allow for a wide-ranging exploration of emergent themes.

This study aimed to explore the decision-making process that a cohort of acute physicians used to determine when fluid resuscitation was required. Commonalities and differences in approach between different grades of clinician were also explored.

3.2 Methods

3.2.1 Study design

Two potential research methods were considered to generate the qualitative data in this analysis: interviews and focus groups. While focus groups allow data to be generated that reflect the collective views of all participants[72], they were felt to be an inappropriate tool to reflect a clinical decision that is most commonly made individually. As a result, a semi-structured, open-ended interview schedule was developed that was systematic while remaining sensitive to the dynamics of the conversation. This approach aimed to avoid stereotypical answers while still allowing comparisons to be made between interviewees.

The project was registered as a single-site qualitative study performed as part of an educational qualification and so did not require national research approval. The relevant local research approvals were provided by the R&D governance team at University Hospitals Birmingham NHS Foundation Trust (reference number: RRK6288).

3.2.2 Participants and recruitment

All interviewees were employed by Queen Elizabeth Hospital Birmingham (QEHB) and worked as doctors in the Acute Medical Unit (AMU) at the time of the interviews. QEHB is a large university teaching hospital in the West Midlands that provides multiple tertiary and quaternary services. Its AMU houses patients from an unselected general medical take. Written informed consent was obtained from all participants before initiating each interview.

To ensure a wide range of perspectives, criterion sampling was used. Four doctors were interviewed from each of the following grades: foundation year, core trainee, specialist trainee and consultant. Recruitment was halted once saturation was reached. Data saturation is a methodological tool used to define an appropriate sample size. Interviewees are recruited until ongoing data analysis fails to identify new concepts or themes. At this point, saturation is judged to have been reached[73, p. 102-3]. Saturation occurred after fourteen interviews, however, an additional four doctors were recruited to confirm that data saturation had occurred and to balance the grades of doctors recruited through criterion sampling.

3.2.3 Data collection

The interview schedule (see *Appendix 2*) covered a general understanding of associated terminology, the fluid assessment process and the subsequent decision-making processes. Because the NICE guideline CG174[28] and the systematic review described in Chapter 2 both identified fluid responsiveness as a key decision-making tool and because the passive leg raise is a non-invasive approach to identifying fluid responsiveness, questions concerning both were incorporated into the interview schedule. Before data collection, the interview schedule was piloted with two core trainees. No significant changes were made so the pilot data were included in the analysis.

To account for the intense work environment of the clinicians being interviewed, the interview was designed to fit a time frame of 15–20 min. Because the author of this thesis developed theoretical positions and values in relation to fluid resuscitation during the completion of the systematic review, a medical student with limited clinical

experience was recruited to conduct the interviews to limit bias during data collection. The medical student received training in interview techniques before study commencement. The interviews were audio-taped, performed in private and transcribed verbatim by the author of this thesis while ensuring anonymity.

3.2.4 Data analysis

Braun and Clarke's 6-step approach to thematic analysis[74] was used as a framework to analyse data from the interviews. Thematic analysis is a method for identifying, analysing and reporting themes within qualitative data and is considered to be a realist method, i.e. one that reports an assumed reality that is evident in the data while avoiding being fixed to a theory or an epistemological position. It, therefore, supported the aims of defining common practices within the setting and allowing flexibility to explore the data without being constrained. In addition, thematic analysis allows the communicated concepts and opinions to be compared with data gathered at different times and in different settings[75]. Thus, it fits well with the data collection process described above.

The author of this thesis and an experienced qualitative researcher individually reviewed transcripts to identify codes and develop emerging themes. The codes were developed both 'horizontally' (by coding each interview as a standalone hermeneutic unit) and 'vertically' (by scanning across the interviews for specific understandings of terminology and commonly used terms surrounding fluid resuscitation and the decision to use it). Through regular meetings during the data collection process between the author and the qualitative researcher, these codes and emerging themes were developed into broader themes until a consistent and

overarching understanding of the decision-making progress underpinning fluid resuscitation was realised. In reporting the findings, direct quotes were used. These have been anonymized given the relatively small number of participants that the research drew from.

3.3 Results

A total of 18 clinicians (10 female; 55.6%) participated in the study: 2 core trainees were interviewed as part of a pilot of the topic guide and a further 4 were recruited from each of the following grades: foundation year, core trainee, speciality trainee, consultant (see Table 1). No staff members declined to participate.

Level of training	**Consultant**	**ST**	**CT**	**FY**
Anonymised Label	Dr A, B, C, D	Dr E, F, G, H	Dr I, J, K, L, M, N	Dr O, P, Q, R

Table 3.1: Anonymised labels for interviewees. The grades of the clinicians identified by their anonymised labels.

Through thematic analysis, five themes related to the decision-making process were identified and explored: (1) the sick patient, (2) the pro-fluid tendency, (3) the relationship between what is taught and what is done, (4) flexibility versus standardisation and (5) the importance of reassessment. Each of these themes is expanded upon below.

3.3.1 The sick patient

For all interviewees, fluid resuscitation was an emergency treatment that aimed to treat hypovolaemia and return a patient's blood volume to its premorbid state. Hypovolaemia was seen as an "extremely common" (D) condition on the acute medical unit. When interviewees were asked for its meaning, they gave a standard medical definition: "reduced intravascular volume" (D). However, when interviewees used the term while describing their decision-making process, it took on a much broader meaning. It became a cypher for two heuristics that underpinned the decision to give fluid resuscitation for all interviewees: how sick the patient was and whether the blood pressure was low.

There was a strong connection between fluid resuscitation and the sick patient. This was not unexpected as fluid resuscitation is an emergency treatment. Yet interviewees consistently stated that being sick was their primary reason for giving fluid resuscitation. This relationship was also implied through the use of related terminology. The ABCDE acronym, for example, which is taught to doctors internationally as a structure for managing critically unwell patients, was mentioned by all but two interviewees as a means of supporting the decision-making process.

The threshold for how sick a patient had to be to receive fluid resuscitation varied markedly between interviewees. For some interviewees, hypotension was required to identify the patient as sick and justify fluid resuscitation ("…the really sick patient is hypotensive." G). However, for others being in hospital was enough.

Subthemes	Quotations
Sick patients require fluid resuscitation	"When a patient is very sick in front of you, you kind of recognise that they are dehydrated and they need fluid resuscitation." (A) "In essence, I think what it comes down to is if a patient is sick enough to require admission to hospital, and as part of that their intravascular status and blood pressure, cardiac output and end-organ perfusion is compromised, a majority of my patients will get some IV [intravenous] resuscitation." (N)
Hypotension defines the sick patient	"The really sick patient is hypotensive. Obviously, I have to give him fluid for this is fluid resuscitation. But if it's, if it's someone who is haemodynamically stable but still needs a bit of fluid, I would go through his medical records and make sure his heart is alright." (G)

Table 3.2: Representative quotations for theme 1. Key quotations that represent the subthemes within theme 1: the sick patient.

As well as being a marker of how sick a patient was, hypotension was an indication for fluid resuscitation in its own right. One interviewee felt that a deranged blood pressure, described as a haemodynamic compromise, was the only "absolute trigger" (P). Blood pressure was particularly useful because it offered a "quantitative value" (Q) that simplified the decision-making process. Several interviewees also mentioned heart rate. Despite that, the presence of tachycardia was never used as an indication for fluid resuscitation in its own right. It was only mentioned alongside blood pressure as a means of validating a decision that had already been made.

3.3.2 The pro-fluid tendency

Interviewees were more equivocal when describing parameters that would stop them from prescribing fluid resuscitation. While all interviewees gave a detailed list of the possible harms of excessive fluid resuscitation, only one interviewee named a

scenario in which they “wouldn’t prescribe fluid” (O). All others couched their answer with words such as “cautious” (J) and “hesitant” (K). When pressed on whether there was a piece of data that would stop them from giving fluid resuscitation, one interviewee responded: “No, I'm extremely pro-fluids.” (B) suggesting there might be an ‘anti-fluid’ cohort of clinicians. No evidence for such a cohort was found though, and the belief that fluid resuscitation was almost always the correct treatment was universal. One interviewee suggested that it was the urgency of the situation that made the described harms less relevant.

Subthemes	Quotations
Fluid overload does not stop fluid from being given to sick patients	“So I think it depends how critically unwell they are with it, and if they look like they're in shock and they're really tachycardic then I would just be giving that [fluid resuscitation] and trying to resuscitate their blood pressure and if it's a less acute situation, like if someone is just dehydrated, then I think you have to weigh up the benefit of giving it against the risk of giving it so you might want to go a little bit more slowly in a slower bag so that you're not causing harm.” (M)
Fluid overload reduces the rate and volume of fluid resuscitation	“There's very little, if anything, I can think of that would absolutely stop anyone from giving some fluid. But certainly, there are conditions…where you have to be very cautious about how much you give. So if somebody is in advanced heart failure and they've already got a degree of oedema or they've got advanced kidney disease on dialysis. Yes, you would be more cautious but that kind of means you decrease the amount of fluid you give and you maybe give it over a longer period rather than it being an absolute contraindication to IV fluids in of themselves.” (N)

Table 3.3: Representative quotations for theme 2. Key quotations that represent the subthemes within theme 2: the pro-fluid tendency.

Instead of stopping interviewees from giving fluid resuscitation, conditions associated with fluid overload led to reductions in the amount and the rate of fluid resuscitation. The prescribed volume was affected by attributes such as the patient's age or weight. Older and frailer patients who were underweight required smaller volumes of fluid at a slower rate, for example. Underpinning this was the belief that small volumes of fluid were always safe. Larger volumes, however, had to be considered more carefully. A maximum amount of fluid of between two and four litres was described by several interviewees.

Once the decision to give fluid resuscitation was made, interviewees searched for other data, such as blood tests, to support their decision. However, they would ignore the results if they did not support the decision, i.e. their function was to support a decision that had already been made.

3.3.3 The relationship between what is taught and what is done

As interviewees described their decision-making processes, they frequently commented on how and where they learned about fluid resuscitation. This learning took place in two phases: at medical school and, later, as a doctor. At medical school, interviewees were taught a structured approach to fluid assessment along with the relevant physiology. Learning as a doctor led interviewees to redesign and streamline their approach through experiential learning and interactions with senior colleagues.

Subthemes	Quotations
The structured 'proper' assessment is learnt at medical school	"We generally learn at medical school that, you know, we start at the end of the bed and then come in close. You look at the hands and the peripheral signs before moving to the face, the chest, the abdomen and then I think most people have a routine that works for them." (N) "So, if you were doing a proper fluid assessment, it would start by generally looking at the patient. So, have they got dry mucous membranes is one thing… However, I think in practice it's not great and not really done." (I) "I don't think it's taught in terms of fluid resuscitation very well." (M).
The limited assessment is learnt through experiential learning	"So a great thing that I heard from one of my previous consultants in T&O was you assess the condition of the patient and then you assess the patient." (P) "I've learned it from experience really by looking at other people and doing it by myself." (G)
Clinical examination should be performed but is not useful	"And then clinical examination. I find it's not particularly helpful in assessing volume status. Apart from cap refill. But we very rarely use it to be perfectly honest because if someone's cold, which invariably quite a lot of old people are, it is of little less value. (C) "It's [skin turgor] not such a helpful test but it's something I normally do." (L)
History-taking is important but should be delayed if the patient is sick	"History-taking will come in the first line for everything." (K) "Depending on how the patient is, if he's really unwell then the history will have to come a bit later." (K) "Septic shock patients, when they come in, just decide to treat them without the need of any history or anything. Just see them, assess them, because these are patients who are very sick, so you just give them a lot of fluids." (A)

Table 3.4: Representative quotations for theme 3. Key quotations that represent the subthemes within theme 3: the relationship between what is taught and what is done.

This streamlined ‘limited’ assessment was closely aligned with the decision-making process that is described above (i.e. the identification of a sick patient). However, when discussing their learning as a medical student, many interviewees began to contradict themselves. While the structured assessment that was taught at medical school was seen as a “proper fluid assessment” (I), it was simultaneously noted to be ineffective and rarely used. Some interviewees explained this contradiction by criticising the teaching they received at medical school.

These comments were most frequently linked to clinical examination with one interviewee noting that they didn’t use clinical examination as it was “not particularly helpful in assessing volume status…” (C). Others also felt that clinical examination was unhelpful but noted they would perform aspects of it as if it was a ritual. This view was not universal, however. One interviewee noted that “physical examination is probably the thing that would sway me the most.” (D).

History-taking provided another source of contradiction. Less than half of the interviewees mentioned history-taking in any form when describing their decision-making process. Yet, when subsequently asked: “Under what circumstances would you use history-taking tools when doing a fluid assessment?”, all noted that it was a vital part of their assessment process.

After stating that history-taking should always come first, some interviewees explained its omission from their decision-making process because of the urgency of the scenario, i.e. because the patient was sick. It was considered to be an

assessment tool “for stable patients rather than acute patients” (H). As a result, it was acceptable to delay history-taking or to omit it altogether. One interviewee asked: “Am I okay to take the history or do I need to quickly assess this patient acutely?” (R) as if the two actions were mutually exclusive.

3.3.4 The transition from standardisation to flexibility

While interviewees shared the same core decision-making process, they sat at varying places along a spectrum between a flexible approach and a standardised approach that remained the same regardless of the scenario.

For some interviewees, such a flexible approach was a crucial part of effective decision-making. This was particularly true at consultant grade – all four consultants commented on the importance of flexibility in their decision-making. Three interviewees used the same phrase, “hard and fast”, to highlight this.

This flexibility was justified because of the variability that existed between different patients and between the different settings and specialities in which the clinician was working. Patient variability was most commonly linked to a patient’s age but could also occur due to comorbidities or the presenting complaint. Variability between settings occurred due to the different assessment tools that were available and differences in the amount of time clinicians were able to spend with each patient. Intensive care was often contrasted to “constrained environments” such as the emergency department where the information to guide the decision-making process and the time with each patient were limited. As a result, rapid assessment

approaches such as “eyeballing” (C) and heuristics such as the use of “gut feeling” (J) were used.

Subthemes	Quotations
Experienced clinicians adopt a flexible approach to decision-making	“I don't think there is a hard and fast rule about how you do things it's based on experienced judgment and, and just using the tools that you have around you to work in a very flexible way. We don't have the luxury of being able to look after a patient in an intensive way hour by hour minute by minute so that's…the way things are. So that's where a constrained environment can…can tend to influence the way you deal with resuscitation.” (C)
Junior clinicians prefer a standardised approach to decision-making	“If I'm worried and someone is clinically unwell I'm going through my A to E approach. There's generally an order.” (N)
Fluid assessments are challenging leading to an accepted uncertainty and lack of competence	“Umm. It's difficult to pin it down to one thing really.” (Q) “I'm not entirely sure we've…we've [sic] understood that process well enough.” (C) “I think overall fluid is not dealt with well…” (J)

Table 3.5: Representative quotations for theme 4. Key quotations that represent the subthemes within theme 4: the transition from standardisation to flexibility.

In contrast to those who preferred a flexible approach, other interviewees highlighted the importance of a standardised decision-making process. As discussed above, frequent reference was made to the ABCDE acronym, the underlying aim of which was to reduce the uncertainty that surrounded emergency scenarios and the use of fluid resuscitation.

Regardless of their preference for flexibility versus standardisation, all interviewees acknowledged the existence of variability and its connection to the uncertainty that permeated the decision-making process. Fluid resuscitation was widely considered to be “a tricky assessment” (D). Of note, this uncertainty was never an individual failing. It was always described as a general lack of understanding that affected all clinicians. Furthermore, all grades of interviewee were comfortable expressing this perceived lack of competence as if it was an accepted part of clinical practice.

3.3.5 The importance of reassessment

Reassessment was widely considered to be a useful way of addressing the aforementioned uncertainty. For all interviewees, reassessment meant repeating the initial assessment to confirm that fluid resuscitation was the right treatment. Some interviewees specifically linked the use of reassessment to acute specialities: “it is very common in people who deal with sick people more.” (G).

The term “fluid responsiveness” was frequently used as a synonym for any improvement following fluid resuscitation. This improvement was most commonly described as a rise in blood pressure, but a patient could also be considered fluid responsive if other improvements were seen. One interviewee defined fluid responsiveness as a gradual improvement in renal function. This was in contrast to the formal definitions for fluid responsiveness which require a percentage rise in haemodynamic function over minutes.

Subthemes	Quotations
Fluid responsiveness describes a patient who has improved with fluid resuscitation	“If it was low blood pressure and I'm trying to see if they’re fluid responsive, then I'd give fluid and see. If it was a renal failure which we think is secondary to dehydration then I would give fluid and see if that improves. That would be the way that I would think about it.” (I). “You can give fluid challenges but always with an endpoint. So what am I trying to fix? Am I chasing a urine output or blood pressure or a heart rate? Have clear goals and if you don't achieve them then have another plan or a plan B.” (J).
Fluid responsiveness can justify stopping fluid or giving more fluid	“So generally if we give a bolus over 15 minutes then we should see an immediate response and if there's no response then that's a sign that they're still deplete and let's give another one and then reassess.” (Q). “If there was an improvement I would, depending on the mean arterial pressure, I would either give them another bolus or get them on maintenance fluids.” (O).
The passive leg raise manoeuvre is rarely used	“I think some of it [why PLR isn’t used] is that people don't know about it. And some of it might be just perception. That seems like an odd thing to do, especially if people are unwell, to go around lifting people’s legs up and seeing what happens. But I mean it makes sense. But I think if you can imagine that if you were the only person that was starting to try to do it then it would seem like a really odd thing to do. You'd have to explain yourself a lot of times a lot of people I think.” (E). “It might give you an idea that someone could be fluid responsive you're giving them sort of an autotransfusion or a challenge from their legs. I think that it does still needs to be in your mind. It's not an exact science. Everyone who does not have a blood pressure rise on passive leg raise may not be euvolaemic. You could have a lot of false negatives if you use that as a test.” (J).

Table 3.6: Representative quotations for theme 5. Key quotations that represent the subthemes within theme 5: the importance of reassessment.

There was less agreement about what should be done once a patient had been identified as fluid responsive. For some, fluid responsiveness was evidence that more fluid was required. For others, it suggested the opposite. One interviewee implied that the presence of fluid responsiveness was less relevant than the “mean arterial pressure” (O), adding weight to the importance of the sick patient as described above.

While fluid responsiveness was recognised by all interviewees, they were less familiar with the passive leg raise (PLR) manoeuvre: an assessment tool recommended by NICE to identify patients who are fluid responsive. Four interviewees had not heard of it, six believed it to be a treatment for hypotension rather than an assessment tool and six were aware of it but did not use it in clinical practice. Of these six, three had never seen it in clinical practice and three had only seen it used in an intensive care setting. One interviewee did not use it because they were concerned that patients would think it an odd thing to do.

Two interviewees had used the PLR as an assessment tool but neither used it routinely. One questioned its accuracy because of a high risk of false negatives. As a result, they were reluctant to be guided by the test if it advised against giving fluid resuscitation, further evidencing the existence of the “pro-fluid” culture that was mentioned above.

3.4 Discussion

This study explored the decision-making process that acute physicians use to determine when fluid resuscitation is required. The process was underpinned by a simple heuristic: whether the patient was sick. The inductive approach used also led to a broader exploration of how the variability that exists during the decision-making process is managed. In addition, it explored how clinicians are taught to prescribe fluid resuscitation and how different modes of learning impact their clinical practice.

3.4.1 Defining the sick patient

How interviewees identified a sick patient was variable, although blood pressure was the most commonly mentioned variable. Other approaches included more intuitive strategies, such as eyeballing or gut feeling. Regardless of how a sick patient was defined, it was clear that the frequent use of the term ‘sick’ reflected a belief that acutely unwell patients require fluid resuscitation. Once a patient had been identified as ‘sick’, a widely held belief that fluid resuscitation was almost always the correct treatment (i.e. a ‘pro-fluid’ culture) continued to support the decision to give fluid even if signs of fluid excess were present.

While no other qualitative study has explored the justification for fluid resuscitation, a post-hoc analysis of the indications for fluid resuscitation used in the CLASSIC trial[76] showed similarities to the findings summarised above. The CLASSIC trial[77] was a feasibility study set in intensive care that randomised 153 patients with septic shock to receive fluid restriction or standard care. The most common indication for fluid boluses in the trial was hypotension (49.6%). A further 9.3% of boluses were given due to tachycardia and 10.6% were given due to a clinical sign. Of interest, 36% of

patients in the fluid restriction group received fluid boluses outside the protocol, offering a real-world example of the 'pro-fluid' culture.

3.4.2 Approaches to managing variability and uncertainty

The variability inherent in the decision to give fluid resuscitation was a recurring theme throughout the interviews. Two opposing decision-making approaches for managing this variability were discussed: flexibility and standardisation. The preference for one or the other seemed to be affected by the grade of the interviewee. Junior grades were more likely to voice a preference for a standardised approach to decision-making, particularly the ABCDE assessment, as a way of reducing the complexity caused by the variability. On the other hand, all four consultants commented on the importance of flexibility and adjusting one's approach to decision-making. This flexible approach was also justified by the variability.

A recent multi-methods study of 549 UK doctors and medical students[78] echoed these findings when it explored decision-making approaches at three career stages: first and final year medical students and experienced doctors. When tackling complex decisions, experienced doctors were more likely to adopt a flexible approach that relied on judgement, a skill that was learnt through experience in the workplace. In contrast, medical students preferred to rely on a fixed set of rules or processes. However, this approach changed during medical training. While first-year students saw rules and guidelines as mandatory for good practice, and were keen to be taught the 'best' approach', final-year students acknowledged that guidelines could not cover all eventualities. This suggested a transformation was taking place during medical training. As they become more senior, students changed from a rule-

based decision-maker to one that recognised the need for nuance and flexibility, much like the transformation described by this study: from the standardised approach used by junior doctors to the flexible approach advocated by the consultant cohort.

Regardless of their seniority, all interviewees noted that the decision to give fluid resuscitation was 'tricky' and were comfortable expressing feelings of uncertainty, suggesting it was a state that was both common and socially accepted in this cohort. Multiple other authors have also noted the ubiquity of uncertainty in medicine and acknowledged its impact on clinical decision-making[79-81]. Clinicians that work in pressured environments with high degrees of complexity and risk, such as acute medical settings, have a higher tolerance for uncertainty[82]. Whether the interviewees selected acute medicine because of a pre-existing tolerance for uncertainty or whether they developed this tolerance as a result of working in acute medicine is unclear.

A scoping review of 19 articles aimed to explore the effect of uncertainty on decision-making[83]. It found that uncertainty can arise from treatments with an unclear probability of success, scenarios with a high degree of complexity and from a lack of evidence to support the clinical decision. This is notable because all three of these sources of uncertainty are present when considering fluid resuscitation. The review also noted that in urgent scenarios clinicians must choose between making a decision with limited information or delaying the decision with potentially negative consequences. This offers one explanation of why the rapid 'limited' assessment process was preferred over the 'proper' assessment and also supports the finding

that, despite being considered vital to an assessment process, history-taking was delayed or omitted by most interviewees.

Reassessing the patient was the most commonly described approach for managing the uncertainty surrounding the decision to give fluid resuscitation. The term ‘fluid responsiveness’ was frequently used during these discussions. It acted as a shorthand for any improvement following fluid resuscitation, even if it took place over days. There was no consensus regarding what should be done for a fluid responsive patient. Both the presence and the absence of fluid responsiveness were used to justify more fluid resuscitation. However, it was never used to stop giving fluid, providing further evidence for the existence of a ‘pro-fluid’ culture.

3.4.3 The ‘proper’ fluid assessment

Two broad types of fluid assessment were described during the interviews: a limited assessment that provided information for the decision-making process and a ‘proper’ assessment. The limited assessment collected a limited number of observations to determine if the patient was ‘sick’ and was acquired through experiential learning by observing more senior colleagues. Because of its close association with the flexible approach to decision-making, it was “difficult to pin down to one thing” (Q).

Alternatively, the ‘proper’ fluid assessment involved an easily-described sequence of clinical examinations occasionally supplemented by observations and history questions that did not vary according to the clinical scenario. As with the standardised approach to decision-making described above, the ‘proper’ fluid assessment was closely associated with teaching at medical school.

Of note, all but one interviewee implied or overtly explained that the ‘proper’ fluid assessment wasn’t relevant to their decision-making process. Despite this, it was still performed by many interviewees as if it was a non-functional but mandatory ritual. In fact, despite emphasising the importance of flexibility in their decision-making process, three consultants continued to perform the ‘proper’ fluid assessment with one remarking that clinical examination was the most important part. Given that senior clinicians are responsible for teaching medical students, this offers an explanation for why the ‘proper’ fluid assessment continues to be taught despite a widespread view that it is ineffective.

3.4.4 Study Limitations

Several limitations should be acknowledged when considering the results. First, the study was carried out in a single site. As a result, these findings should be considered in the context of the setting (a university teaching hospital in the West Midlands) and it should not be assumed that the data capture the views of clinicians in other hospitals. This is not a limitation *per se* but rather a function of the constructivist paradigm that the methodology is built upon. Because the data is a co-creation between the interviewer and the interviewees, the results could differ if conducted by another researcher in another setting at another time.

In addition, the qualitative interview methodology relies on the respondent’s ability to accurately and honestly recall details about their working practices. There are multiple psychological, social and cultural factors that may make this challenging. To ameliorate these factors, all interviews took place in private and were conducted by a

medical student, reducing the impact of the social desirability bias[84] (the tendency of respondents to answer questions in a manner that will be viewed favourably by others). However, despite these efforts, the described decision-making processes may differ from those used in reality.

It is also possible that the interview process did not capture all of the relevant views that existed in the setting. Several steps were taken to reduce this risk. Criterion-based sampling was adopted to ensure the perspectives from a range of clinicians with different experiences of fluid resuscitation were recruited. In addition, data collection was continued until saturation was reached.

Finally, the author of this thesis is an acute physician with pre-defined views of fluid resuscitation and so there is a potential for bias. To reduce this risk, an experienced qualitative researcher supported the design and analysis of the data. Furthermore, data analysis was carried out independently and then collectively, allowing a process of reflection that challenged many of the assumptions that might have led to bias while limiting the subjectivity of the analysis.

3.5 Conclusion

The decision to prescribe fluid resuscitation is heavily influenced by the identification of a patient as sick and by the assumption that fluid resuscitation is almost always the correct treatment. As the experience of a clinician builds, the decision-making process transitions from a fixed, standardised process that is perceived to be non-functional (labelled the ‘proper’ fluid assessment) to an approach that is flexible and can adapt to the variability inherent in clinical medicine. Despite this transition, the

‘proper’ fluid assessment continues to be taught at medical school and experienced clinicians continue to advocate for its use.

4 Discussion: Connecting the guidelines to the literature and current practice

4.1 Summary of the main findings

This thesis has summarised the evidence for diagnostic tests that determine a need for fluid resuscitation and also explored the decision-making process underpinning the prescription of IV fluid.

The systematic review has highlighted the importance of fluid responsiveness in the academic literature concerning the assessment for fluid resuscitation in patients appropriate for admission to acute medicine. However, no evidence was provided to support the widespread assertion that fluid responsiveness was equivalent to a need for fluid resuscitation. In addition, only a small number of relevant studies were found. Furthermore, the studies' samples were small, the design was heterogeneous and the risk of bias was high. This prevented meaningful comparisons.

The qualitative data demonstrated that the concept of the 'sick patient' was a key part of the decision-making process for fluid resuscitation with hypotension a frequent means of defining when a patient was sick. Simple heuristics, e.g. eyeballing and gut feeling, were also commonly used by all grades of doctor. Of note, hypotension was also the most common reason for patients to be included in studies in the systematic review, corroborating its importance as a prompt for fluid resuscitation.

4.2 Work-as-done versus work-as-imagined

Two approaches to fluid assessment were identified through analysis of the qualitative data. The limited assessment was developed through experiential learning and was built around the identification of a patient as sick. Conversely, the 'proper' assessment was taught at medical school and involved a stereotyped list of history questions and examination findings that was widely considered to be unrelated to the decision to give fluid resuscitation.

Both types of assessment have similarities with concepts that are well-described in patient safety literature: work-as-done and work-as-imagined[85]. Work-as-done is the reality of what happens. It is a series of processes that constantly adapt due to the variability that exists in the workplace, particularly in complex systems such as healthcare[86]. Because of this variability, experienced practitioners (such as the consultant grades in the qualitative study) transition to using more flexible approaches to work (such as the limited fluid assessment and the flexible approach to decision-making).

Work-as-imagined is a theoretical construct that can be described as the work that people are supposed to do[85]. It is often defined by leaders and managers rather than front-line workers so may not reflect what actually happens. However, it is far easier to describe and conceptualise than work-as-done. As a result, it is often used to create guidelines and protocols.

This definition of work-as-imagined has notable similarities with the 'proper' assessment. Many interviewees felt it was what they should be doing. As a result,

they continued to perform it even though it did not affect their decision-making process and the perception of its importance was expressed by all seniorities, including consultant grades. So, while the decision-making process of senior clinicians transitioned to a flexible decision-making approach that was informed by a limited fluid assessment, the consultants' perception of what should be done remained rooted in what they had been taught at medical school.

The high degree of importance that senior doctors continue to place upon the 'proper' fluid assessment may explain why it continues to be taught to all grades of doctor-in-training[68-70] even though the majority of interviewees described it as unhelpful. This raises questions about how much of the medical curriculum is also seen as mandatory and simultaneously ineffective.

4.3 The Guidelines

As discussed, the processes defined by work-as-imagined often underpin clinical guidelines. However, this was not apparent for the fluid resuscitation recommendations found within NICE CG174[28]. As per the algorithm displayed in *Figure 1.2* (p 5), the guidelines advised using an "ABCDE approach"[28, p. 38] to determine if the patient was hypovolaemic and required fluid resuscitation. This approach has more in common with the limited fluid assessment and the identification of the sick patient than it does with the 'proper' fluid assessment.

Because of the limited evidence base that was noted by the systematic review, the GDG decided that "a formal clinical evidence approach to this question [how to perform a fluid assessment] was not appropriate"[28, p. 70]. Consequently, they formed

their recommendations through consensus opinion alone. In short, this means the guidelines are a reflection of the beliefs of the GDG, a collection of experienced doctors, rather than a synthesis of the current evidence base. It seems logical, therefore, that the recommendations within NICE CG174[28] have more in common with the decision-making processes used by the consultants in the qualitative study than those described by the academic literature identified by the systematic review.

Once fluid resuscitation is given, the guidelines advise that a series of undefined reassessments should take place. This recommendation is also closely related to the findings of the qualitative study while differing from the concepts described in the academic literature. During the interviews, the phrase 'fluid responsiveness' was synonymous with the concept of reassessment. It was a broad term that could describe any patient improvement, including a haemodynamic improvement over minutes or an improvement in renal function over days. This was in contrast to the way the phrase was used in the literature. Each of the included studies in the systematic review defined fluid responsiveness in a specific manner. However, the definition of fluid responsiveness varied markedly between studies – 13 different definitions were used by the 14 included studies. The heterogeneity in the meaning of 'fluid responsiveness' in both the systematic review and the qualitative study underlines the need for a standardised definition before the concept can be translated into a useful assessment tool.

4.4 Strengths and limitations

The strengths and limitations of this thesis have been discussed at the end of each chapter. They are summarised and expanded upon below.

The broad eligibility criteria in the systematic review limited the generalisability of the findings to an acute medical population and contributed to a heterogeneity that prevented comparison between studies. However, this approach to study selection was warranted by the limited evidence base – an issue which was also acknowledged by the NICE CG174 GDG.

It should also be noted that limiting the systematic review to diagnostic test accuracy studies led to a focus on bedside investigations. As the qualitative study demonstrated, a flexible combination of simple heuristics (e.g. eyeballing) and basic observations (e.g. blood pressure) drives the decision-making process for fluid resuscitation in the acute medical setting. It may be that studies exploring these alternative assessment approaches exist but were not identified by the systematic review.

The qualitative study was completed in a single site, involving doctors working in the same department. Therefore, it should not be assumed that the findings of the study capture the views of clinicians in other specialities or other hospitals. In addition, the working practices that were described by the interviewees may differ from those they use in reality. This is a known limitation of the interview process and is also a concept that is recognised in the patient safety literature: work-as-disclosed. This concept is defined as a description of working practices by those who do the work[87]. It is a proxy for work-as-done and may differ from what is actually done for a variety of reasons, highlighting the challenge of defining work-as-done.

4.4 Research recommendations

This thesis has highlighted multiple research opportunities that can and should be pursued. Fluid responsiveness is an ill-defined but commonly mentioned term in the academic literature and in national and international guidelines. For this reason, a consensus definition that is feasible outside of the intensive care setting should be agreed upon as a priority.

Once an appropriate consensus definition exists, relevant observer variability data should be gathered for each measurement and measurement tool. Then, the proportion of well and acutely unwell adults who are fluid responsive should be described. During this process, consideration should be given to the impact of factors such as disease severity, age and comorbidities. Furthermore, the prevalence of fluid responsiveness in different aetiologies of shock should be studied.

With these data, appropriately powered observational studies should be designed to examine potential associations between fluid responsiveness and commonly used outcome measures. As discussed above, because studies have previously described fluid responsiveness in health, it may simply be a marker of cardiac function. Following this, randomised-controlled trials can be designed to measure the impact of using fluid responsiveness in various clinical settings. Finally, to support the integration of fluid responsiveness into clinical practice, a wider understanding of the decision-making process used by doctors is required to clarify the exact purpose of fluid responsiveness and to support GDGs in incorporating the test into an appropriate point in their algorithms.

The qualitative data has also left several unanswered questions that warrant further exploration. How do doctors identify a sick patient? Why is the ‘proper’ fluid assessment advocated by clinicians who also describe it as ineffective? Where and why does the medical school curriculum different from current medical practice?

These questions should be addressed through a wider exploration of work-as-done and work-as-imagined in the acute medical setting. Reconciling the gaps between these two concepts could lead to further insights into the ways in which clinicians adjust, adapt and organise their decision-making processes in an uncertain environment. With this information, guidelines and protocols will be better able to reflect the variability that exists in a complex adaptive system such as healthcare and, therefore, will be better able to inform clinical practice.

5 Conclusion

The data presented in this thesis suggest that the best approach to fluid resuscitation assessment remains unclear. While fluid responsiveness is widely regarded as a solution to this problem, the systematic review has demonstrated that there is no agreement on how it should be defined and a weak evidence base to support its use.

Despite this, the findings of the qualitative study and their similarities with the guidelines suggest that a wealth of experience exists which has supported clinicians in developing streamlined, flexible decision-making processes suitable for the variability and uncertainty inherent in acute medicine. It remains unclear, however, whether these processes are helpful or harmful for patients who receive fluid resuscitation.

Further research is required to define and test these decision-making processes. If they are effective, this will ensure that they are formally recognised in the literature and will support educators in stepping away from the mandatory yet ineffective clinical rituals that still exist in the medical curricula.

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Appendix 1: Search strategy for Medline

1. sepsis.ti,ab
2. septic.ti,ab
3. septicaemia.ti,ab
4. septicemia.ti,ab
5. mods.ti,ab
6. multiple organ dysfunction syndrome.ti,ab
7. mof.ti,ab
8. multiple organ failure.ti,ab
9. sirs.ti,ab
10. systemic inflammatory response syndrome.ti,ab
11. exp Systemic Inflammatory Response Syndrome/
12. exp Multiple Organ Failure/
13. **OR/1-12 (196,454 on 7/2/17; Search repeated on 14/6/18)**
14. fluid* ADJ3 replace*.ti,ab
15. fluid* ADJ3 resuscitat*.ti,ab
16. fluid* ADJ3 infus*.ti,ab
17. fluid* ADJ3 administrat*.ti,ab
18. fluid* ADJ3 restor*.ti,ab
19. volume ADJ3 replace*.ti,ab
20. volume ADJ3 resuscitat*.ti,ab
21. volume ADJ3 infus*.ti,ab
22. volume ADJ3 adminstrat*.ti,ab
23. volume ADJ3 restor*.ti,ab

24. intravenous* ADJ3 fluid*.ti,ab
25. IV fluid*.ti,ab
26. colloid*.ti,ab
27. crystalloid*.ti,ab
28. hypertonic solution*.ti,ab
29. hypertonic saline.ti,ab
30. isotonic solution*.ti,ab
31. isotonic saline.ti,ab
32. ringer*.ti,ab
33. hartman*.ti,ab
34. albumin*.ti,ab
35. gelatin*.ti,ab
36. dextran*.ti,ab
37. starch*.ti,ab
38. exp Fluid Therapy/
39. exp Plasma Substitutes/
40. exp Infusions, Intravenous/
41. exp Colloids/
42. exp Hypertonic solutions/
43. **OR/14-42 (489,435 on 7/2/17; Search repeated on 14/6/18)**
44. inpatient*.ti,ab
45. in-patient*.ti,ab
46. patient ADJ3 admiss*.ti,ab
47. patient ADJ3 admit*.ti,ab
48. hospital*.ti,ab

49. intensive treatment unit*.ti,ab
50. ITU.ti,ab
51. intensive care.ti,ab
52. ICU.ti,ab
53. critical care.ti,ab
54. “accident and emergency”.ti,ab
55. emergency department*.ti,ab
56. emergency room*.ti,ab
57. exp Inpatients/
58. exp Hospitalization/
59. exp Intensive Care Units/
60. exp Critical Care/
61. exp Emergency Service, Hospital/
62. exp Hospital Departments/
63. exp Internal Medicine/
64. **OR/44-63 (2,591,320 on 7/2/17; Search repeated on 14/6/18)**
65. **AND/13,43,64 (4,231 on 7/2/17; Search repeated on 14/6/18, 221 records between 2017 to Current)**

Appendix 2: Interview schedule

What do you understand by the term fluid resuscitation?

- Could you summarise that in a short definition?

What do you understand by the term hypovolaemia?

- Could you summarise that in a short definition?

What would initially make you think of doing a fluid assessment on a patient?

Please could you talk me through how you assess a patient who is hypovolaemic?

- Would you perform any other assessments?
- Could you tell me more about why you do that?
- (If interviewees don't mention the physical examination) What steps would you go through in a physical examination?
- Under what circumstances would you use history-taking tools when doing a fluid assessment?

What is the order in which you would usually go about this process?

How do you use the information you've collected to decide whether intravenous fluid resuscitation is needed?

Would there be any signs, symptoms or comorbidities that would discourage you from prescribing fluids?

Could you talk me through the potentially detrimental effects of prescribing fluids?

- Are there any others?

Do you use a test for fluid responsiveness to support your fluid assessment?

- How commonly do you see other doctors use this method of assessment?
- Is it something that you think is taught in clinical training?

How might the ‘passive leg raise’ manoeuvre aid your fluid assessment?

- Can you tell me more about that?
- How commonly do you see other doctors use this method of assessment?
- Is it something that you think is taught in clinical training?

Where did you learn about the passive leg raise manoeuvre?