HARRY PERKINS INSTITUTE OF MEDICAL RESEARCH

Royal Perth Hospital

REstricted **F**luid **RE**suscitation in **S**epsis associated **H**ypotension (REFRESH)

A pilot randomised clinical trial

Dr Stephen Macdonald

on behalf of the REFRESH Investigators

THE UNIVERSITY OF WESTERN AUSTRALIA

CCREM Centre for Clinical Research in Emergency Medicine

Disclosure

Trial funded by the Emergency Medicine Foundation
Royal Perth Hospital and other participating institutions

Endorsed by the ACEM Clinical Trials Group

Critical Care Medicine®
Society of Critical Care Medicine
The Intensive Care Professionals

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

"We recommend that in the resuscitation from sepsis-induced hypoperfusion, at least 30ml/kg of intravenous crystalloid fluid be given within the first 3 hours".

Crit Care Med 2017;45:486-552

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The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 30, 2011 VOL. 364 NO. 26

Mortality after Fluid Bolus in African Children with Severe Infection

Maitland et al NEJM 2011;364:2483-95

SYSTEMATIC REVIEW

Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis

Jonathan A. Silversides[1,2*], Emmet Major[2], Andrew J. Ferguson[3], Emma E. Mann[2], Daniel F. McAuley[1,4], John C. Marshall[5,6], Bronagh Blackwood[1] and Eddy Fan[5]

N=2051/11 trials

Conservative fluid strategy:

- No mortality effect
- Increase vent-free days
- Reduced ICU stay

Predominantly ICU trials

Intensive Care Med 2017;43:155-170

Aims

To assess the **feasibility** of a regimen of **restricted fluid volume** and **early vasopressor** among patients in the emergency department with suspected **sepsis** and **hypotension**

Methods

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Multicentre, open-label, randomised clinical trial

- The Prince Charles Hospital
- Gold Coast University Hospital
- The Austin Hospital
- Royal Hobart Hospital
- Armadale Health Service
- Fiona Stanley Hospital
- Royal Perth Hospital
- Sir Charles Gairdner Hospital

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Inclusion and exclusion criteria

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Inclusions

1. Suspected or proven infection
2. Systolic blood pressure <100mmHg following at least 1000ml IV crystalloid

Exclusions

1. > 2000mls fluid administered (including pre-hospital)
2. Requirement for urgent surgery
3. Age <18 years
4. Pregnant
5. Patient in extremis requiring immediate intervention
6. Patient wishes or comorbidities such that either inotrope support or fluid resuscitation contraindicated

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Outcomes

Primary

- Total fluid volume from ED arrival to 6 hours

Secondary

-Total fluid volume to 24 hours

- Organ failure
- Mortality
- Protocol compliance
- Adverse events

Sample size = 100

- 90% power to detect 4.2L v 2.8L/6h
- α=0.05

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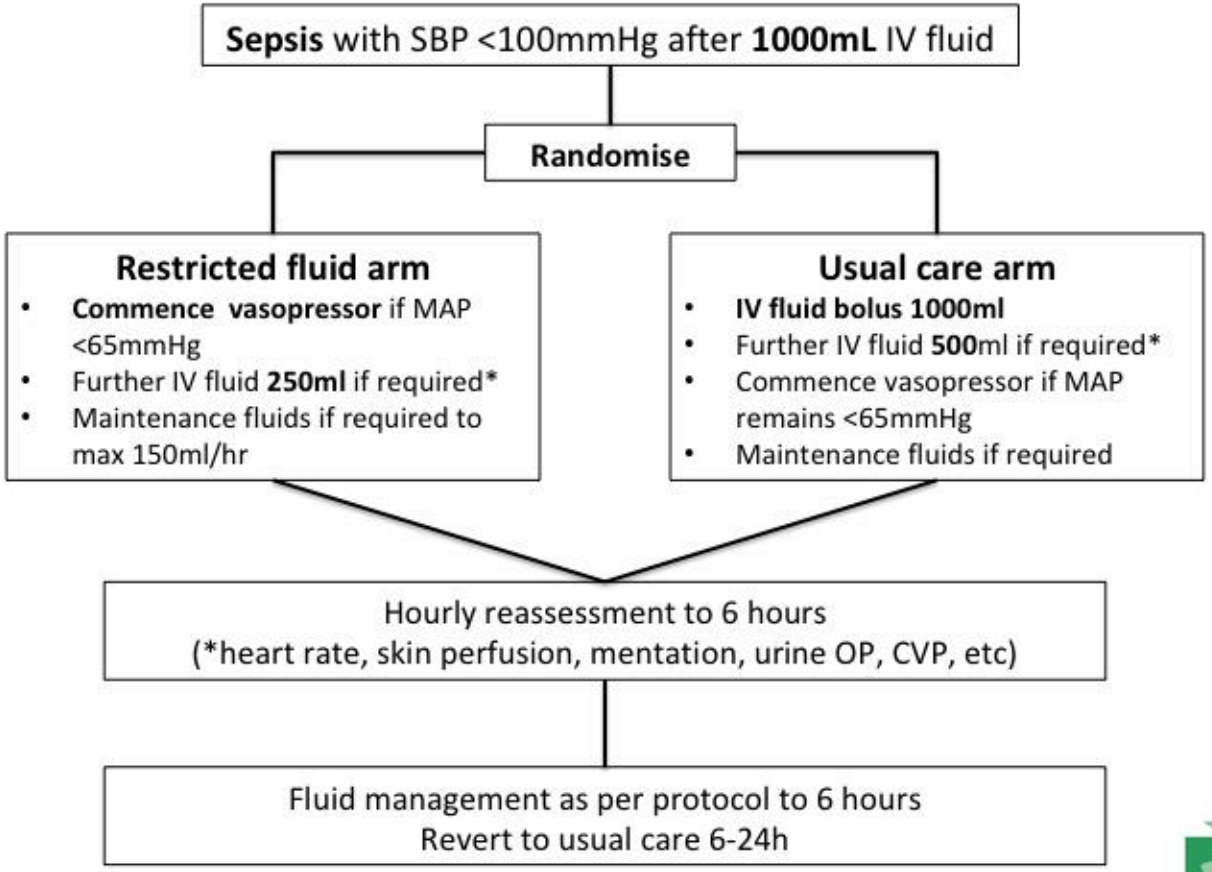

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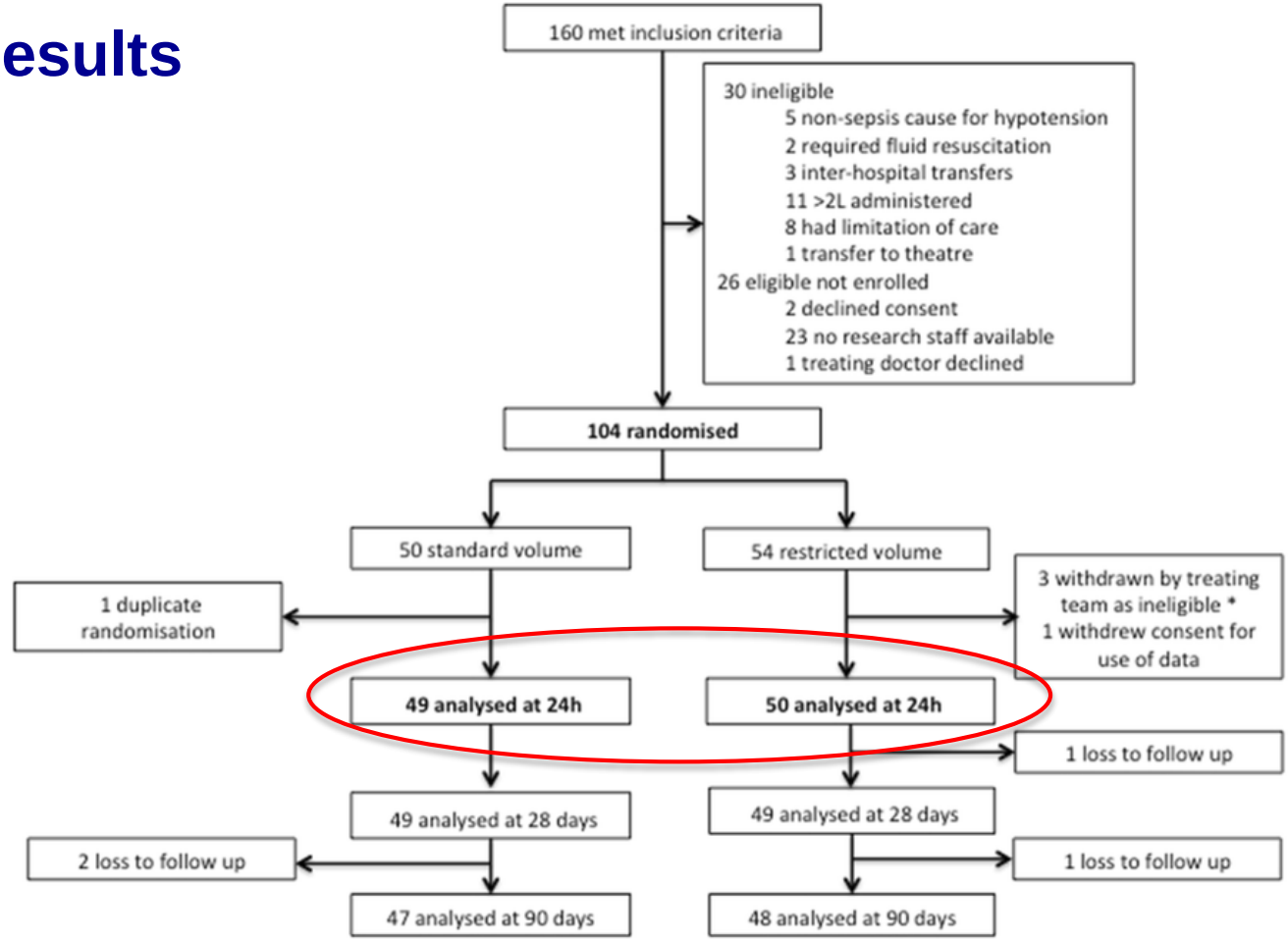
Results


160 met inclusion criteria
30 ineligible
5 non-sepsis cause for hypotension
2 required fluid resuscitation
3 inter-hospital transfers
11 >2L administered
8 had limitation of care
1 transfer to theatre
26 eligible not enrolled
2 declined consent
23 no research staff available
1 treating doctor declined
104 randomised
50 standard volume
54 restricted volume
1 duplicate randomisation
3 withdrawn by treating team as ineligible *
1 withdrew consent for use of data
49 analysed at 24h
50 analysed at 24h
1 loss to follow up
49 analysed at 28 days
49 analysed at 28 days
2 loss to follow up
1 loss to follow up
47 analysed at 90 days
48 analysed at 90 days

Baseline characteristics

	Usual Care N=49	Restricted volume N=50
Age (years)	66 (45, 76)	66 (52, 78)
Male Sex n (%)	30 (61)	31 (62)
Weight (kg)	72 (64, 90)	80 (66, 88)
Mean SBP (mmHg)	87±9	86±9
Lactate (mmol/L)	1.8 (1.2, 2.6)	1.7 (1.1, 3.5)
Charlson score	2 (0, 4)	2 (1, 4)
APACHE II score	14 (10, 18)	15 (10, 20)
SOFA score	5 (4, 7)	5 (3, 9)
Acute Kidney Injury N (%)	30 (60)	26 (52)
Pre randomisation fluid (ml)	1250 (1000, 2000)	1450 (1000, 1500)
Time from ED arrival (minutes)	143 (89, 250)	140 (103, 214)

Data are median (Q1, Q3)

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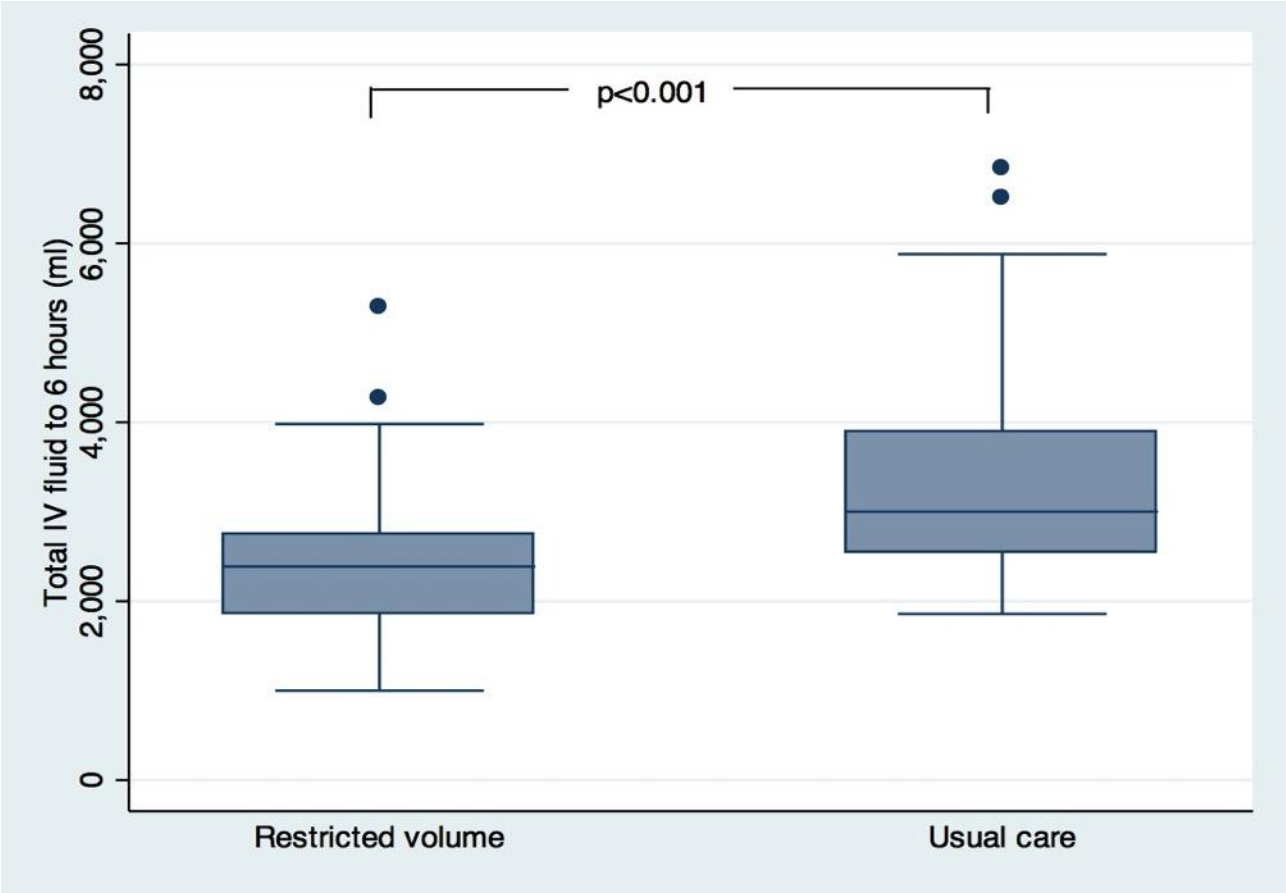
Fluids to 24 hours

	Usual Care N=49	Restricted volume N=50	P value
T0-T6 (ml)	1715 (1017, 2500)	968 (625, 1458)	<0.001
T0-T6/kg (ml)	23 (15,33)	12 (7,20)	<0.001
Total prerandomisation-T6 ml	**3000 (2550, 3900)**	**2387 (1750, 2750)**	**<0.001**
Total to T6/kg (ml)	43 (35, 50)	30 (23, 39)	<0.001
T6-T24 (ml)	1000 (428, 1743)	1134 (500, 2000)	0.73
Total prerandomisation-T24 (ml)	**4250 (3450, 5207)**	**3543 (2443, 4410)**	**0.005**
Total to T24/kg (ml)	61 (46, 79)	40 (31, 64)	0.005

Data are median (Q1, Q3)

Fluid volume to 6 hours



Vasopressor use

	Usual Care N=49	Restricted volume N=50	P value
Vasopressor in ED N (%)	23 (47)	36 (72)	0.011
Vasopressor at 24h N	19 (39)	24 (48)	0.35
Time to start vasopressor (mins):	150 (63, 224)	34 (15, 88)	0.001
Central venous access N (%)	20 (41)	26 (52)	0.42
Volume prior to vasopressor (ml)	2000 (2000, 2777)	1400 (1000, 1700)	<0.001
Duration of vasopressor (hours)	33 (15, 50)	21 (9, 42)	0.13
Peak vasopressor dose*	0.18 (0.1, 0.43)	0.11 (0.08, 0.22)	0.14

Data are median (Q1, Q3)

Clinical outcomes

	Usual Care	Restricted volume
In hospital N	**49**	**50**
ICU Admission N (%)	29 (59)	33 (66)
Ventilated N (%)	9 (18)	10 (20)
Duration of ventilation (h)	24 (12, 80)	13 (6, 41)
RRT N (%)	4 (8)	4 (8)
90 days N	**47**	**48**
Alive hospital free days	82 (76, 85)	83 (78, 86)
Died N (%)	3 (6)	4 (8)

Data are median (Q1, Q3) or as stated

Adverse events

	Usual Care (N=49)	Restricted Volume (N=50)
Complications related to central venous access N (%)	2 (4)	1 (2)
Complications related to extravasation of peripherally administered vasopressor N (%)	0	0
Complications of fluid overload e.g. acute pulmonary oedema N (%)	1 (2)	1 (2)
Complications related to ischaemia N (%)	1 (2)	2 (2)
Total number with SAE (%)	**4 (8)**	**4 (8)**

Protocol deviations

	Usual Care (N=49)	Restricted Volume (N=50)
None N (%)	38 (76)	44 (88)
Did not receive minimum 1000ml in standard volume arm N (%)	6 (12)	_
Administered >3250ml in restricted volume arm N (%)	_	1 (2)
Transferred to theatre N (%)	3 (6)	2 (4)
Clinical decision for limitation of care post-randomisation N (%)	2 (4)	3 (6)
Total number with one or more protocol deviations N (%)	**11 (22)**	**6 (12)**

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Discussion

- Reduction in fluid volumes at 6 and 24 h
- Lower than expected volume in usual care arm
- No signal for harm
- Implications for a future phase III trial

Intensive Care Med
https://doi.org/10.1007/s00134-018-5433-0

ORIGINAL

Restricted fluid resuscitation in suspected sepsis associated hypotension (REFRESH): a pilot randomised controlled trial

Stephen P. J. Macdonald[1,2,3*], Gerben Keijzers[4,5,6], David McD Taylor[7,8], Frances Kinnear[9], Glenn Arendts[1,2,10], Daniel M. Fatovich[1,2,3], Rinaldo Bellomo[11], David McCutcheon[1,2,3,12], John F. Fraser[13], Juan-Carlos Ascencio-Lane[14], Sally Burrows[2], Edward Litton[15], Amanda Harley[4], Matthew Anstey[16], Ashes Mukherjee[12] and for the REFRESH trial investigators

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Next steps: ARISE FLUIDS Collaboration

- Australia and New Zealand EM and ICU research team with international collaborators

- Programmatic approach
  - ☑ Survey of current practice
  - ☐ Observational study – *in progress*
  - ☑ Pilot RCT
  - ☐ Phase III RCT – planned, funding pending

Investigators and participating institutions

REFRESH

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TASMANIAN HEALTH SERVICE

Tasmanian Government

Gold Coast Health
Building a healthier community

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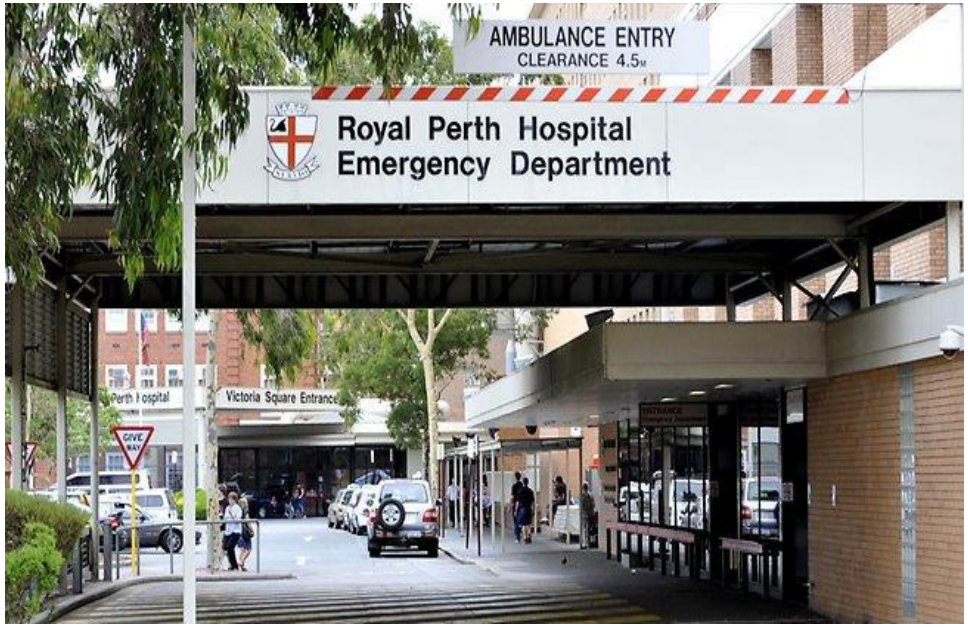

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