Appendix 8

Question 21: data extraction tables

Akech *et al.* 2010[49]

Data extraction table

Reference and design	Intervention	Participants	Outcome measures
Author: Akech *et al.*[49] *Year:* 2010 *Country:* Kenya *Study design:* RCT (phase II) *Setting:* inpatient (district hospital) *Number of centres:* one *Funding:* the Wellcome Trust (Sponsor: Oxford University)	*Intervention:* RL (see below for dosages) *Control:* WHO fluid resuscitation regimen (HSD/5D) (see below for dosages) *Third treatment arm:* 4.5% HAS for those with non-diarrhoeal shock Children with severe dehydrating diarrhoea/ shock were randomised to RL or HSD/5D; children with presumptive septic shock (non-diarrhoeal shock) were randomised to RL, HSD/5D or HAS. Paper only reports mortality and safety outcomes for HAS group owing to small numbers ($n=6$) *Other interventions used:* all children treated according to WHO guidelines – hypoglycaemia treated ORS (ReSoMaL) given where appropriate, all received antibiotics, early nasogastric feeding withheld but maintenance i.v. dextrose fluids given until stabilised, intestinal ileus excluded and tolerance of oral feeds established (see below for further details)	*Definition of SAM:* any of: ■ W/H *z*-score <-3 or W/H percentile 70% ■ MUAC <11.0 cm ■ oedema involving at least both feet (kwashiorkor) *Number of participants:* 86 assessed for eligibility, 61 enrolled and randomised (RL $n=29$, HSD/5D $n=26$, HAS $n=6$) *Sample attrition/dropout:* no withdrawals/dropouts; 31/61 (51%) deaths *Sample crossovers:* none *Inclusion criteria:* aged >6 months with SAM, with evidence of shock. Shock criteria included children with more than one of the following: CRT >2 seconds, lower limb temperature gradient, weak pulse volume, deep 'acidotic' or 'Kussmaul' breathing, creatinine >80 µmol/l, or depressed conscious state [prostration (inability to sit up if aged >8 months)] if present after correction of hypoglycaemia *Exclusion criteria:* severe anaemia (Hb ≤ 5 g/dl), pulmonary oedema (defined as clinical evidence of presence of fine crepitations in both lung fields plus oxygen saturations $<90\%$ in air), raised intracranial pressure, known congenital heart disease *General characteristics of participants:* SAM children aged >6 months with hypovolaemic shock secondary to either dehydrating diarrhoea or sepsis, 42% HIV+ve	*Primary outcomes:* resolution of features of shock [including tachycardia and oliguria (production of abnormally small volume of urine)] at 8 and 24 hours *Secondary outcomes:* ■ adverse events ■ mortality *Method of assessing outcomes*: resolution of shock defined as the absence of all of: severe tachycardia (heart rate >160 beats/minute), CRT >2 seconds or oliguria (urine output <1 ml/kg/hour). Dehydrating diarrhoea defined as ≥ 6 watery stools per day MUAC measured with a cloth (non-stretchable) measuring tape; weight with an electronic scale (Soehnle model 7300; CMS Instruments, UK) and length using a measuring board of standard design Temperature gradient defined as cooler extremities to warmer core, and was assessed by running the back of the palm of the hand up the lower limb. Radial pulse was used to assess pulse volume. Oxygen saturation continuously measured using a multichannel Siemens® monitor. Blood pressure and urine output monitored hourly and then every 4 hours after 8 hours Adherence to protocol validated by an internal, but independent monitoring team *Adverse symptoms:* respiratory distress, pulmonary oedema, allergic reaction (to HAS) *Length of follow-up:* outcomes at 24 hours; reports that children were followed up intensively up to 48 hours and thereafter for in-hospital survival *Recruitment dates:* November 2006 to May 2008 (recruitment discontinued early)

© Queen's Printer and Controller of HMSO 2012. This work was produced by Picot *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

Characteristics of participants:

Characteristic	RL (*n* = 29)	WHO fluid HSD/5D (*n* = 26)	*p*-value
Severe dehydration/ shock,[a] *n* (%)	21 (72)	19 (73)	NR
Presumptive shock,[b] *n* (%)	8 (28)	7 (27)	NR
Male, *n* (%)	17 (59)	15 (58)	0.94
Age, months (IQR)[c]	16 (6)	15 (14)	0.41
MUAC cm, mean ± SD	10.0 (1.9)	10.4 (1.4)	0.43
W/H *z*-score, mean ± SD	–3.9 (1.0)	–3.4 (1.3)	0.18
Severe wasting, *n* (%)	21 (72)	14 (54)	0.15
Kwashiorkor, *n* (%)	4 (14)	8 (31)	0.19
HIV+ve,[d] *n* (%)	14 (48)	9 (35)	0.65
WHO shock criteria, *n* (%)	23 (79)	18 (69)	0.39
Tachypnoea (> 60 breaths/minute), mean ± SD	13 (45)	16 (62)	0.22
Severe tachycardia (> 160 beats/minute), mean ± SD	8 (28)	11 (42)	0.25
Hydration, *n* (%)			
Reduced skin turgor	16 (55)	8 (31)	0.07
Sunken eyes	19 (66)	11 (42)	0.08

Comments: baseline characteristics data not presented in the paper for HAS group owing to small numbers, though described as similar to other participants with sepsis

- *Whole-group characteristics:* median age was 15 months (IQR 12–23 months). Thirty-five children (64%) had severe marasmus, 13 (21%) had features of oedematous malnutrition (kwashiorkor) and 41 (75%) fulfilled the strict WHO definition of advanced shock
- Children with severe shock/dehydration (owing to diarrhoea) had a significantly higher frequency of WHO SAM shock definition than children with presumptive sepsis shock [32/40 (80%) vs 10/21 (48%), respectively; $p = 0.01$]. The diarrhoeal group were also more severely acidaemic (pH 7.22 ± 0.19 vs 7.34 ± 0.17, respectively; $p = 0.03$)
- The mean (± SD) volume for the bolus infused was 39 ml/kg (± 22) and 30 ml/kg (± 10) for RL and HSD/5D groups, respectively

Other baseline characteristics such as severity of shock (e.g. deep breathing, hypoxia, tachycardia, etc.), consciousness, biochemistry and laboratory variables were presented, but have not been data extracted

Results

Primary outcomes	RL (*n* = 29)	WHO fluid HSD/5D (*n* = 26)	*p*-value
Number with shock, *n*/*N* (%)			
8 hours	14/25 (56)	15/22 (68)	0.39
24 hours	14/25 (56)[e]	14/18 (78)	0.14
Oliguria (< 1 ml/kg/hour), *n*/*N* (%)			
8 hours	3/25 (12)[f]	9/22 (41)[g]	0.02[h]
24 hours	6/25 (24)[i]	8/18 (44)[j]	0.16
Tachycardia (> 160 beats/minute), *n*/*N* (%)			
8 hours	4/25 (16)	6/22 (27)	0.34
24 hours	4/25 (16)	8/14 (44)	0.04

Comments: there appear to be discrepancies in the paper between data presented in tables and data presented in figures, all estimated by reviewer (see table footnotes for details)

- Authors report that a larger decline in the proportion with shock was observed in children who received RL vs HSD/5D, particularly in the diarrhoeal group. However, the differences were NS at any time point [table 2 and figure 2 (line graph) in publication]
- Median AUC for the hourly urine output was significantly lower in HSD/5D participants compared with RL: 51 ml/kg/hour (IQR 36–116 ml/kg/hour) vs 101 ml/kg/hour (IQR 63–141 ml/kg/hour), respectively, Kruskal–Wallis chi-squared = 4.6; $p = 0.03$
- Median AUC for heart rates were similar for both study interventions (Kruskal–Wallis chi-squared = 0.3; $p = 0.59$)
- Paper also reports results for creatinine, but these have not been extracted here

Secondary outcomes	RL ($n = 29$)	WHO fluid HSD/5D ($n = 26$)	4.5% albumin (HAS) ($n = 6$)	p-value
In-hospital mortality, *n*/*N* (%)	13/29 (45)	15/26 (58)	3/6 (50)	0.62[k] 0.34[l]
Tachypnoea (> 60 breaths/minute), *n*/*N* (%):				
8 hours	2/25 (8)	7/22 (32)	NR	0.04
24 hours	3/25 (12)	7/18 (39)	NR	0.04

Comments:

- Of the children who died, 26/31 (84%) fulfilled the WHO malnutrition shock definition at admission. Case fatality rate in this high-risk subgroup was 59% (26/44), irrespective of allocated intervention and was associated with an increased risk of death (RR 2.0, 95% CI 0.92 to 4.36; $p = 0.05$) compared with those who did not have this criteria
- In those with severe diarrhoea, mortality was higher in HSD/5D than RL group [13/19 (68%) vs 9/22 (43%) respectively; $p = 0.11$], but the difference was NS. [Reviewer note: possible error in text – RL should be 9/21 (43%)]
- In those with presumptive shock (non-diarrhoeal shock), mortality was 2/7 (29%) in HSD/5D vs 4/8 (50%) in RL group, again the difference was NS ($p = 0.61$) (note: there is a possible error reported in the publication for presumptive shock for HSD/5D)
- Nine out of 13 (69%) of children with kwashiorkor died irrespective of treatment arm. Deaths of children with kwashiorkor were 29% of the total deaths. Kwashiorkor was associated with a non-significant increased risk of death [OR 2.2 (95% CI 0.7 to 10.1); $p = 0.14$]
- Twelve out of 31 (39%) of deaths occurred within 24 hours of recruitment, whereas 16 out of 31 (52%) occurred within 48 hours of enrolment. On Kaplan–Meier survival analysis, there was no significant difference in time to death when any of the intervention fluids were used for resuscitation (log-rank test combined $p = 0.42$)
- Mean respiratory rate was significantly greater in the HSD/5D arm than RL arm at 8 hours and 24 hours ($p = 0.002$). (Reviewer: table 2 in paper reports $p = 0.04$ separately for 8 hours and 24 hours)
- Overall, there was a trend towards higher median AUC of respiratory rates in those who died (2262; IQR 1938–2897) compared with survivors (2015; IQR 1547–2391), but did not reach statistical significance (Kruskal–Wallis chi-squared = 3.6; $p = 0.06$)
- Paper also reports data for resolution of base deficit (acidosis), but these have not been extracted here

Safety:

- No child developed clinical features of pulmonary oedema or allergic reaction (to HAS) during the course of study observation
- Frusemide or other diuretics were not required or prescribed during the trial
- There were no differences in the mean (± SD) sodium concentration at admission (133 ± 11 vs 134 ± 10; $p = 0.81$), 8 hours (134 ± 10 vs 139 ± 10; $p = 0.09$) and 24 hours (138 ± 9 vs 140 ± 9; $p = 0.47$) between those who received HSD/5D and RL, respectively

HIV:

- Thirteen (42%) of those who died were HIV+ve, 14 (45%) were HIV–ve and four (13%) declined HIV tests
- Infection with HIV did not significantly increase the risk of death [OR 1.18 (95% CI 0.38 to 3.72); $p = 0.76$]

Barriers to implementation

Participant recruitment was discontinued early after an interim review of the safety data and thus the study was underpowered

© Queen's Printer and Controller of HMSO 2012. This work was produced by Picot *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

Methodological comments

Allocation to treatment groups: children were randomly assigned in two batches (1) those with severe dehydration/shock randomised to WHO HSD/5D or RL; and (2) those with presumptive (non-severe diarrhoea) shock randomised to WHO HSD/5D, RL or HAS. Random allocation was assigned by use of sealed cards. No further details were reported

Blinding: reports that study interventions were not masked (thus patients and care providers were not blinded). No details on blinding of outcome assessors

Comparability of treatment groups: no statistically significant differences between RL and HSD/5D treatment groups (*p*-values reported). Paper reports that baseline characteristics and disease severity indices were similar across the fluid intervention arms. Also, characteristics and haemodynamic responses in the six HAS individuals were similar to the other participants in the presumptive sepsis shock group who were randomised to HAS/5D and RL treatments (data were not presented because of small numbers)

Method of data analysis: the null hypothesis was that there is no difference in the safety profile or effect on physiological parameters of shock when using any of the three fluids for resuscitation. Dichotomous and categorical variables were created from continuous variables. Derived variables were created from clinical factors defined by guidelines as indicating a definitive need for urgent therapeutic intervention and for lab variables. Means and SDs were calculated for continuous variables using Student *t*-tests. Non-normally distributed data were compared using Sign-rank test and Kruskal–Wallis. Proportions were compared using chi-squared and Fisher's exact tests as appropriate. Kaplan–Meier survival analysis was also used to compare time-to-event (death). AUCs were calculated for serial measurements and their medians compared using Wilcoxon rank-sum and Kruskal–Wallis tests. AUC was employed to compensate for confounding effect of early mortality, hence, missing observations, leading to biases in the highest risk group and resulting in imbalance within the survivors. Reports that all analyses were ITT; outcomes were reported for all those who survived

Sample size/power calculation: the study aimed to recruit 90 children: 45 RL, 45 HSD/5D and 20 HAS (reviewer note: numbers add to 110 not 90) to provide sufficient information on haemodynamic response and adverse events to the two fluid management regimes to understand the potential efficacy rather than for comparison. A specific sample size calculation was not presented. The numbers were not achieved as recruitment was discontinued after an interim review of safety data, and therefore the study was underpowered

Attrition/dropout: numbers and reasons reported. No dropouts/withdrawals and 31 deaths (15 HSD/5D, 13 RL, 3 HAS)

General comments

Generalisability: likely that most of the children would meet the current WHO criteria (W/H *z*-score < -3 SD). Population were largely infants (median age 15 months) with SAM and features of shock (75% had advanced shock as defined by WHO), severe or non-severe diarrhoea, and 42% were HIV+ve

Outcome measures: outcomes appropriate for study objectives; weight gain NR

Intercentre variability: N/A

Conflict of interest: no competing interests declared. All authors were associated with the Wellcome Trust Research Programme, but states that the funders had no role in the research or in the preparation of the manuscript

WHO fluid resuscitation regimen HSD/5D

- Initial bolus of 15 ml/kg over 1 hour
- Repeat bolus given once if some improvement in features of shock noted
- If no improvement seen, 10 ml/kg whole blood transfusion given over 3 hours

RL or albumin (HAS) resuscitation

- Initial bolus of 10 ml/kg over 30 minutes
- Repeated only twice over 1 hour if clinical reassessment demonstrated any of the following features of shock: CRT > 3 seconds, weak pulse volume, temperature gradient or hypotension (systolic blood pressure < 80 mmHg)
- Additional boluses (10 ml/kg over 1 hour) only permitted if oliguria (< 0.5 ml/kg/hour) or hypotension (systolic blood pressure < 80 mmHg) developed (20 ml/kg over 1 hour). Maximum bolus volumes given were 40 ml/kg

- At each clinical review, children were assessed for clinical resolution of shock and examined for signs of pulmonary oedema (if present, further boluses withheld and treated with diuretics)
- No invasive monitoring, such as central venous pressure measurement, was used
- Children did not receive inotropes, vasopressors or hydrocortisone
- Other than initial fluid boluses, additional intravenous fluids boluses, intravenous rehydration for children with severe diarrhoea or maintenance fluids were not given (as per guideline recommendation), except if child was intolerant to feeding when low volume maintenance was provided

Standard WHO management of SAM

In all other respects, children were treated according to WHO guidelines

- Hypogylcaemia (blood glucose < 3 mmol/l) treated with 5 ml/kg of 10% dextrose
- Malnutrition ORS (ReSoMaL) given to children with significant diarrhoea (greater than six loose stools/day) rather than i.v. rehydration, irrespective of the level of clinical dehydration
- All children received i.v. ampicillin (50 mg/kg four times/day) and i.m. gentamicin (7.5 mg/kg once daily) for at least 5 days
- Ceftriaxone used as second-line antimicrobial or when directed by microbiological results
- Early nasogastric feeding recommended by the guideline immediately after resuscitation was withheld, and children were placed on maintenance i.v. dextrose fluids until children were stabilised, intestinal ileus excluded and tolerance of oral feeds established

Hb, haemoglobin; i.m., intramuscular; NA, not applicable; NR, not reported; NS, not statistically significant.
a Severe diarrhoea.
b Non-severe diarrhoea, per cent calculated by reviewer. The six participants in the HAS (albumin) group all had non-severe diarrhoea (presumptive shock).
c Unclear if this is mean or median.
d Seven children were missing HIV test results: three (10%) RL group and four (15%) HSD/5D group.
e Shown to be approximately 60% at 24 hours in Figure 2 (line graph).
f Shown to be approximately 21% at 24 hours in Figure 3 (line graph).
g Shown to be approximately 46% at 24 hours in Figure 3 (line graph).
h $p = 0.05$ in text.
i Shown to be approximately 38% at 24 hours in Figure 3 (line graph).
j Shown to be approximately 54% at 24 hours in Figure 3 (line graph).
k Comparison of three groups.
l HSD/5D vs RL.

© Queen's Printer and Controller of HMSO 2012. This work was produced by Picot *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.

Quality assessment for primary studies (modified for severe malnutrition)

A. Selection bias

1. Are the individuals selected to participate in the study likely to be representative of the target population?	Very likely ✓	Somewhat likely	Not likely	Cannot tell	
2. What percentage of selected individuals participated?	80–100%	60–79% ✓	<60%	N/A	Cannot tell
Summary of selection bias *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*		

B. Study design

1. What was the study design? (Please tick appropriate and specify design if categorise as 'Other')	RCT			✓
	CCT			
	Cohort analytic (two group pre + post)			
	Case–control			
	Cohort [one group pre + post (before and after)]			
	Interrupted time series			
	Other – *specify*			
	Cannot Tell			
2. Was the study described as randomised?	Yes ✓	No		

If answer to no. 2 is 'no' complete summary then go to section C. Confounders. If answer is 'yes', answer no. 3 and no. 4 below, before completing summary for this section

3. If answer was yes, was the method of randomisation described?	Yes ✓	No	
4. If answer was yes, was the method appropriate?	Yes ✓	No	
Summary of study design *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*

C. Confounders

1. Were there important differences between groups prior to the intervention?	Yes	No ✓	Cannot tell	
2. If yes, indicate the percentage of relevant confounders that were controlled [either in the design (e.g. by stratification or matching) or in the analysis]?	80–100%	60–79%	<60%	Cannot tell
Summary of confounders *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	

D. Blinding

1. Was the outcome assessor aware of the intervention or exposure status of participants?	Yes	No	Cannot tell ✓	
2. Were the study participants aware of the research question?	Yes ✓	No	Cannot tell	
Summary of blinding *(Methodological strength of study)*	*Strong*	*Moderate*	*Weak* ✓	

E. Data collection methods				
1. Were data collection tools shown to be valid?	Yes ✓	No	Cannot tell	
2. Were data collection tools shown to be reliable?	Yes	No	Cannot tell ✓	
Summary of data collection *(Methodological strength of study)*	*Strong*	*Moderate* ✓	*Weak*	
F. Withdrawals and dropouts				
1. Were withdrawals and dropouts reported in terms of numbers and reasons per group?	Yes ✓	No	Cannot tell	
2. Indicate the percentage of participants completing the study (If the percentage differs by groups, record the lowest)	80–100% ✓	60–79%	< 60%	Cannot tell
Summary of withdrawals and dropouts *(Methodological strength of study)*	*Strong* ✓	*Moderate*	*Weak*	
G. Intervention integrity				
1. What percentage of participants received the allocated intervention or exposure of interest?	80–100% ✓	60–79%	< 60%	Cannot tell
2. Was the consistency of the intervention measured?	Yes ✓	No	Cannot tell	
3. Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?	Yes	No ✓	Cannot tell	
H. Analysis				
1. Indicate the unit of allocation	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
2. Indicate the unit of analysis	Community	Organisation/ institution	Practice/ office	Provider	Patient ✓
3. Are the statistical methods appropriate for the study design?	Yes ✓	No	Cannot tell		
4. Is the analysis performed by intervention allocation status (i.e. ITT) rather than actual intervention received?	Yes ✓	No	Cannot tell		
Global rating for study[a] (Overall methodological strength of study – based on sections A–F)	Strong	Moderate ✓	Weak		

N/A, not applicable.

a Strong = four strong ratings with no weak ratings; moderate = one weak rating; weak = two or more weak ratings.

© Queen's Printer and Controller of HMSO 2012. This work was produced by Picot *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health.