Fluid Management in Surgery

FCS SA Intermediate Exam Tutorial

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SBAH

What to discuss?

DISCLAIMER: THIS PRESENTATION IS BASED ON MY PERSONAL INTERPRETATION OF THE AVAILABLE EVIDENCE

- Physiology of Body Fluids
- Composition of common IV Fluids
- Indications for Fluids: Resuscitation (Rehydration), Maintenance & Replacement (prescribing fluids)
- Monitoring Volume Status
- Effects of inappropriate fluid usage
- Crystalloids
- Colloids
- Albumin

PHYSIOLOGY OF BODY FLUIDS

TBW 60% BODY WEIGHT IN ADULTS
(75% NEWBORN, 65% CHILDREN)

EXTRACELLULAR 35%

- INTERSTITIAL ±80%
- INTRAVASCULAR ±20%
- THIRD SPACE

INTRACELLULAR 65%

STARLING EQUATION OF FLUID EQUILIBRIUM

Extracellular loses are compensated by fluid movement from Intracellular space and vice versa
Hydrostatic, Oncotic, Osmotic & Capillary pressures

Endothelial Glycocalyx (EG) Functions

- Regulates Capillary Permeability
- Plays a role in Mechanotransduction: release of NO in response to shear stress (regulates vessel tone)
- Preserve circulatory Microenvironment: multiple molecules require direct interaction with EG for function e.g. Antithrombin, Heparin cofactor II, Tissue factor pathway inhibitor-TFPI, Vascular endothelium growth factor-VEGF, Interleukins (2, 3, 4, 5, 7, 8), Extracellular superoxide dismutase-Ec-SOD and others.

(Procoagulants, anticoagulants, endothelial cell regeneration, leukocyte chemotaxis and diapedesis, scavengers of oxygen radicals)

Endothelial Glycocalyx (EG)

- Glyco-proteins, proteoglycans and soluble components (Albumin) attached to endothelial luminal cell surface
- EXERT ONCOTIC PRESSURE
  - Inflammatory damage to EG causes large heavy molecules to leak into the IS worsening tissue oedema and organ damage
  - Colloids (HES, Albumin) also interact with EG in a complex manner not yet fully clarified in clinical practice (increase or decrease permeability)
  - Linked to and affected by several pathophysiological processes (Diabetes, Atherosclerosis, Ischaemia-reperfusion) [SYSTEMIC ENDOTHELIOPATHY]

Internal Homeostasis

- Maintaining CONSTANT
  - TBW Volume
  - Serum Osmolarity (Na, Glucose, Urea, circulating proteins)
  - Electrolyte concentration (Na, Cl, K, Ca, Mg and others)
  - pH
- Abnormalities are due to deficit (hypovolaemia) or excess (fluid overload)
- In normal state TBW is maintained via balance of input and output and osmolarity-mediated ADH release and function

Input vs Output Adult

Input	Output
• Oral water (free water and water in food) 2000 - 2500 ml/day • Metabolic water (oxidation water) ± 250-300 ml/day	• Urine 1500 – 2000 ml/day (0.5-1ml/kg/h)* • Fecal loses ± 200 ml/day • Respiratory and Sweat loses : variable volume, influenced by ambient temperature, level of physical activity and metabolic rate**
Daily Balance	2000 ± 500 ml

(*) Without use of diuretics
(**) Oxidative water production is increased during catabolic state but is offset by respiratory and skin loses

TBW Regulation: ADH feed-back & Serum Osmolarity

- Normal Serum Osmolarity: 275-295 mOsm

Increased Plasma osmolarity > 300 i.e. Net water loss, Hypovolaemia	R	Decreased Plasma Osmolarity < 270 i.e. Fluid Overload
Stimulates release of ADH from Neurohypophysis	E	Inhibits release of ADH
ADH Stimulates V2 receptors to opens up (express) renal tubular aquaporins	S	Renal tubular aquaporins closed
Aquaporins: Increases tubular water permeability	U	Decreases tubular water permeability
Urinary Water is retained (osmotic reabsorption) Urinary solutes are maintained (Concentrated Urine)	L	Urinary Water is increased with normal solute load (Urine diluted)
Plasma water increases	T	Plasma water decreases
Correction of osmolarity	S	Correction of osmolarity

IV Fluids commonly available in SA

Crystalloids	(Semi) Synthetic Colloids	Natural Colloids
• Ringers Lactate • 0.9% NaCl (Normal Saline) • Plasmalyte B (Balsol) • Rehydration Solution (RHS) • Maintelyte (5%-10%) • 5% Dextrose in Water • 10% Dextrose in Water • 5% NaCl (Hypertonic Saline) • ½ DD (Half Darrow's + Dextrose) • Neonatalyte	Starches (HES) • Voluven • Volulyte Gelatins • Gelofusine	• Human Albumin 4 % (Albusol) • Blood Components: RC, FFP, Platelets, Freeze Dried Plasma • Especial Fractions: Cryoprecipitates, Factor Concentrates (Haemosolvate, Haemosolvex), Immunoglobulins

Composition of Crystalloid Fluids in SA

	Na	Cl	K	Buffer	Ca	Mg	Glucose	pH	Osm	Use
Plasma	135-145	95-105	3.5-5.3	HCO3 24-32	2.2-2.6	0.8-1.2	3.5-5.5	7.35-7.45	275-295	
Ringer Lactate (*)	130	109	4	Lact 28	1.4	0	0	6-7.5	273	Resusc. Replace
NaCL 0.9%	154	154	0	0	0	0	0	4.0	308	Resusc. Replace
Plasmalyte B	130	110	4	HCO3 27-28	0	1.5	0	7.4	273	Resusc. Replace
½ DD	61	52	17	Lact 27	0	0	50g	4.5	434	Resusc. Replace

Electrolytes in mmol/L

(*) Safest Resuscitation fluid in non-bleeding patients

Composition of Crystalloid Fluids in SA

	Na	Cl	K	Buffer	Ca	Mg	Glucose	pH	Osm	Use
Plasma	135-145	95-105	3.5-5.3	HCO3 24-32	2.2-2.6	0.8-1.2	3.5-5.5	7.35-7.45	275-295	
5% Dextrose	0	0	0	0	0	0	50g	4.5	555	Replace
Maintelyte 5% (*)	35	65	25	0	0	2.5	50g	4.0	405	Maint.
Maintelyte 10%	35	65	25	0	0	2.5	100g	4.0	683	Maint.
Dextro-Saline (RHS)	154	154	0	0	0	0	50g	4.0	586	Maint. Replace

Electrolytes in mmol/L

Composition of Crystalloid Fluids in SA

	Na	Cl	K	Buffer	Ca	Mg	Glucose	pH	Osm	Use
5% NaCL	855	855	0	0	0	0	0	4.0	1710	Replace
Neonatalyte 10% (*)	20	21	15	Lact 20	2.5	0.5	100g	4.0	670	Replace
Electrolyte 2 (**)	62	50	25	Lact 25	0	3	100	4.0	723	Replace
8.5% HCO3	1000	0	0	HCO3 1000	0	0	0	0	2000	Replace

(*) Contains HPO_4 3,75 mmol/L
(**) Contains HPO_4 7 mmol/L

Composition of Colloids

Colloid	Main Component	Na – Cl – K – HCO3	Osmolarity/pH	Indications
Voluven (Isotonic)	6 % HES (Potato) 130/0.4	154 – 154 – 0 - 0	308/4.5 – 5.5	Resuscitation
Volulyte (Balanced)	6 % HES (Maize) 130/0.5	137 – 110 – 4 – 34	286.5/5.7 – 6.5	Resuscitation
Gelofusine	4 % Gelatin (Bovine)	154 – 120 – 0 – 0	274/ 7.5	Resuscitation
Albusol 4	4 % Human Albumin	< 130 - < 2 – 0 – 0 Citrate < 4	Hypertonic/7.0	Multiple
Albusol 20	20 % Human Albumin	< 100 - < 10 – 0 – 0 Citrate < 20	Hypertonic/7.0	Multiple

IV Fluid Therapy

- Prescribed every day
- Incorrect dosage and choice of fluid common
- Lack of knowledge (composition and indications)
- Complications
- Understanding indications is essential

Key Concepts in IV Fluid Use

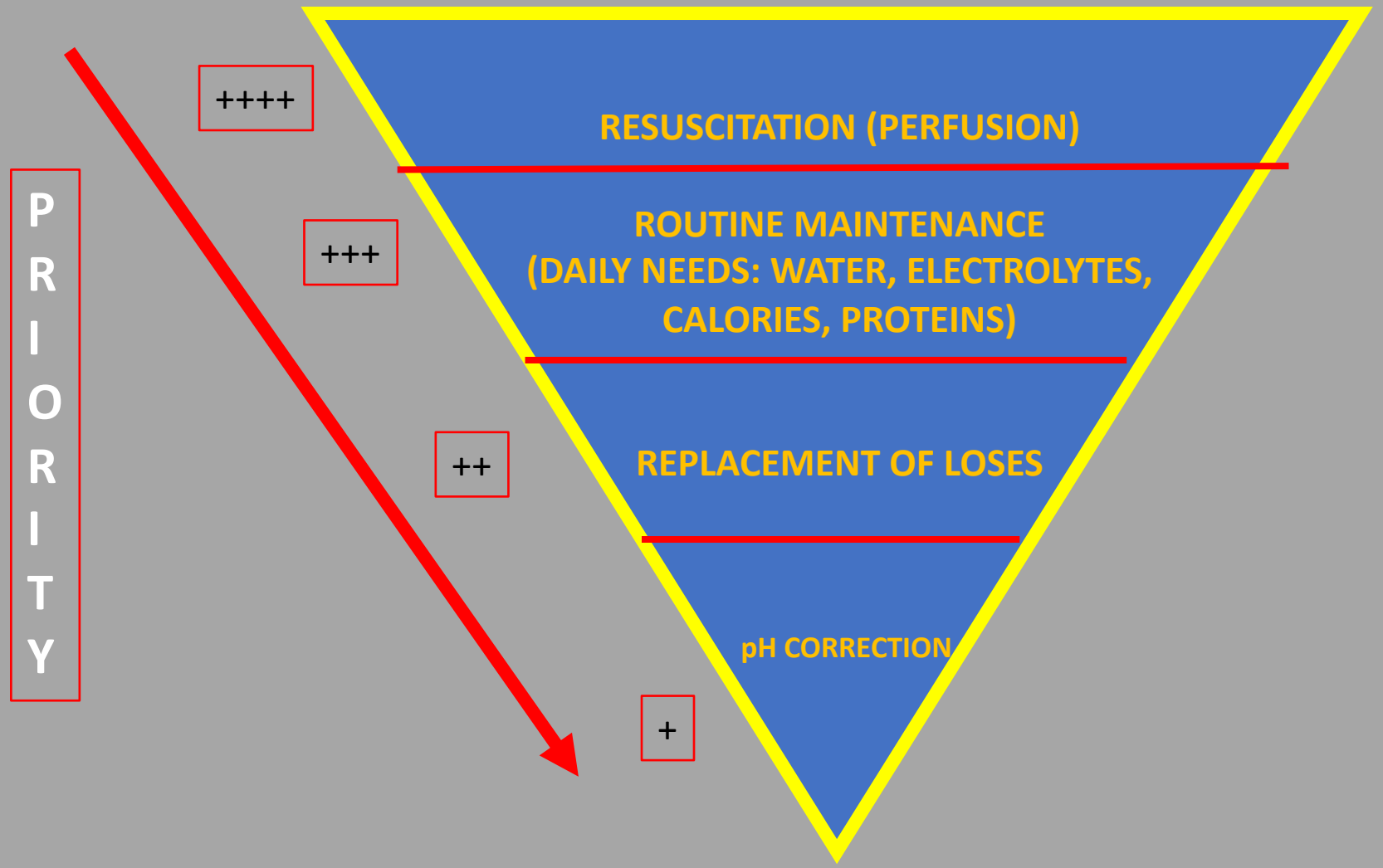
- **Resuscitation**: Plasma expansion to improve tissue perfusion, must contain Na, Isotonic (Ringers, Colloids)
- **Rehydration**: purely to restore water deficits, electrolytes have to be added depending on estimated-calculated deficits
- **Maintenance**: provide basic daily requirements of water, electrolytes and caloric support for patient no able to use oral-enteric route
- **Replacement-Redistribution**: fluids and electrolytes added to or subtracted from Maintenance fluids to restore daily balances in cases with superimposed deficits or excess (e.g. ECF, Ileus)

When using fluids….

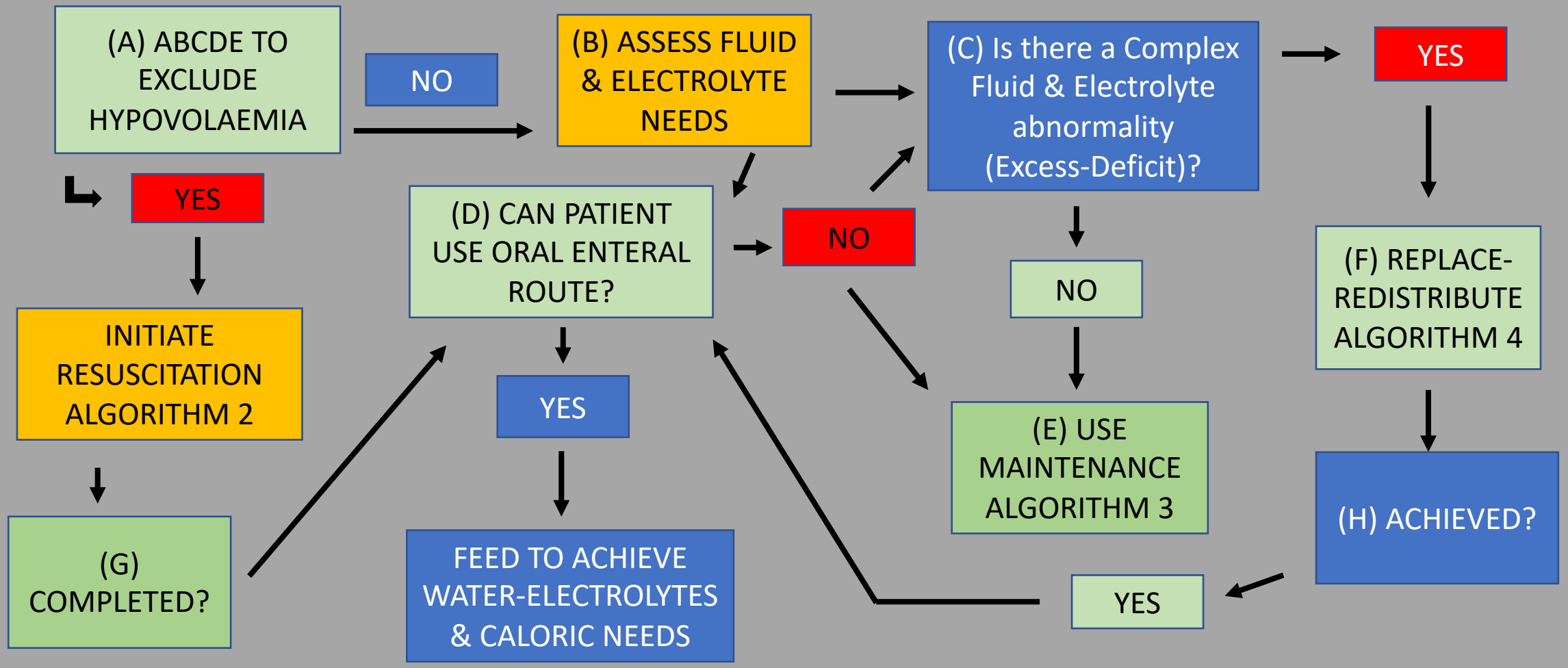
Aim to restore internal homeostasis (balance) of:

- Body Water
- Electrolytes (Na, Cl, K, Ca, Mg, PO4)
- Acid-base balance
- Caloric needs (Carbohydrates-Lipids)
- Protein Needs (essential amino acids)
- Vitamins and Trace elements (Zinc)

Pyramid of Fluid Management



General Assessment Fluid Needs



Assessment of Hypovolaemia

- Volume status: clinical exam, trends and context
- Common clinical tools are generally unreliable in critical illness but may detect early changes and need for advanced monitoring
- Simplest Tool

Urinary Output
Neonates and infant up to 1 y: 2ml/kg/h
Toddlers 12-36 mo: 1.5 ml/kg/h
Children > 3 y: 1 ml/kg/h
Adult: 0.5-1 ml/kg/h

Deleterious effects of Hypovolaemia (Shock)

Hypotension (baro & chemo receptor stimulation) **Adreno-cortical stimulation** **Endogenous Catecholamines, ADH, Cortisol release** **Systemic Vasoconstriction** **Water retention** **Reduced cellular perfusion (poor DO2)** **Anaerobic metabolism (metabolic acidosis)** **Ischemia-reperfusion syndrome**	**Glycocalyx shedding "Systemic Endotheliopathy"** **Activation of Systemic Inflammation (platelets, neutrophils, endothelial cells)** **Vasoplegia** **Hypercatabolism** **Bacterial Translocation** **MOF** **Death**

Clinical “determinants” of Volume Status

Parameters	Measure	Pitfalls
Vital Signs	BP	Could be normal despite volume changes, vasopressor therapy
	Pulse	Influenced by multiple factors: pain, fever, fluid loses, drugs
	Orthostatic BP changes	Affected by IAP, need objective quantification of SVV
Physical Exam	GCS	TBI, drugs
	Capillary Refill	Influenced by environment
	Skin Changes	Influenced by environment
	Limb Temperature	Influenced by environment
	Urinary Output	Stress response, vasopressors, IAP
Laboratory	Na/Urea	Influenced by multiple factors
	Lactate	Abnormally elevated: drugs, vasopressors, liver ischaemia
	ScvO2	Surrogate measure, Influenced by high Hb concentration & SaO2

Monitoring Volume Status

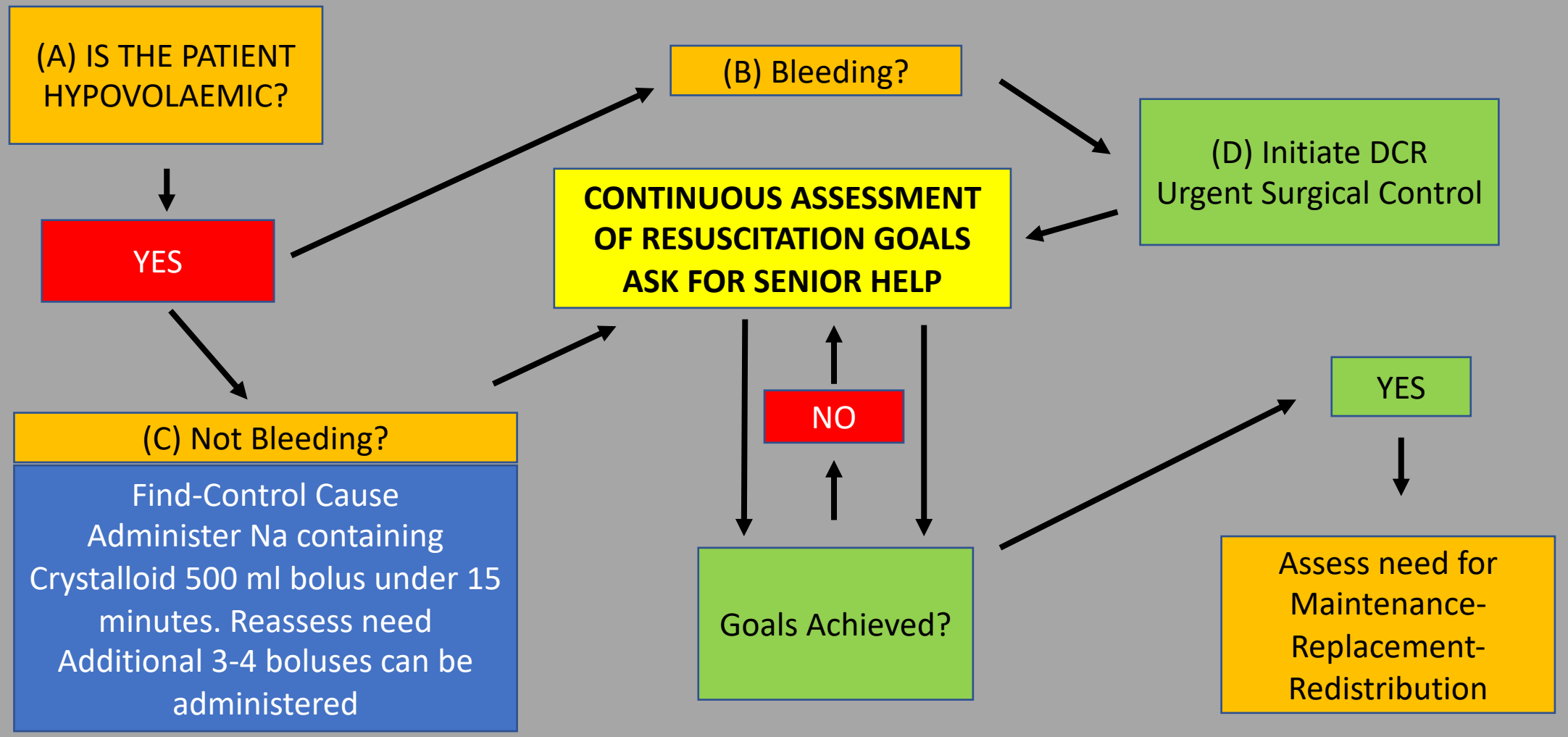
- Non-invasive vs Invasive
- Static vs Dynamic
- Multiple tools available
- Variability of results and poor correlation with actual volume status is common
- Equipment availability
- Use of End-points of resuscitation: “safer” alternative in resources-constrained environments?

Summary of Available Tools

(*) Need FloTrac, PiCCo, LiDOO for SVV measurement

Method	Type	Assess Fluid Responsiveness	Comments
History Findings	Noninvasive, Static	NO	Poor correlation with invasive Press.
Physical exam	Noninvasive Static & Dynamic	YES	Serial exam may detect changes in organ perfusion
Chest X Ray	Noninvasive	NO	No standard measurements of vascular pedicles and CT ratio, serial may help determine effects of Rx
CVP	Invasive Static	NO	Poor correlation with fluid responsiveness
PCWP – PAC	Invasive Static	NO	Poor correlation with fluid responsiveness
TT Echo	Noninvasive Static	NO	Single measure of chamber volume difficult to interpret, serial best, labor intensive
SVV	Invasive Dynamic	YES	Requires sedated, ventilated patient with N VT
Oesophageal Doppler	Invasive Dynamic	YES	Not useful for continuous monitoring
VC diameter by US	Noninvasive Dynamic	YES	Body habitus and operator dependent
Passive leg raising	Noninvasive Dynamic(*)	YES	Affected by IAP
Bioimpedance	Noninvasive Static	NO	Cannon assess intravascular volume

Resuscitation



Resuscitation (Paediatric)

- Ringer Lactate 20 ml/kg boluses (< 40 kg)
- Avoid Hypertonic and Glucose containing solution as plasma expanders
- Hypoglycaemia common especially in neonates, infants and younger children (Monitor Glucose and administer PRN)
- Continuous re-assessment of resuscitation end-points (goals directed)
- Monitor electrolytes, be wary of using IV K^+ without proper monitoring and acceptable urinary output

Routine Maintenance-Adult

- **Prescribe and Administer Daily Fluids and Electrolyte Requirements**(*)

- When a patient cannot meet daily requirements using oral-enteral route but does not have Replacements and Redistribution issues (no fistula, no vomiting, no sepsis, no organ failure, etc.)

(*) Dependent on level of physical activity and environmental factors (ambient Temperature)

Daily Requirements Adult (baseline)

- Water: 30-50 ml/kg
- Na, Cl, K: 1 mmol/kg/day
- ± 2000 Calories/day (0.8 Cal./ml of Water/day (60% Carbs/40% lipids)
- Proteins (> 1.5 g/kg/day)

Some Prescriber Points

- Reassess and Monitor daily (input-output, loses)
- Stop if able to use Oral – Enteric route
- Small bore Tube Naso or Oro-gastric use suggested if Maintenance > 3 days

Adult Maintenance

Fluid	Composition	Comment
Maintelyte 5%	5% dextrose 50g/L Na 35 mmol/L Cl 65 mmol/L K 25 mmol/L Mg 2.5 mmol/L No Buffer	Acid Solution pH 4.0 High Osmolarity 405 mOsm(*) Should be fluid of choice after resuscitation is completed if patient cannot use oral-enteral route for feeding

Routine Maintenance Paediatric

- Isotonic Fluid maintenance to prevent hospital acquired Hyponatraemia secondary to SIADH (AAP CP Guidelines 2018, *Feld LG et al Pediatrics 2018*)
- Monitor and administer Glucose PRN

SIADH induced by:
- Hypertonic fluids
- Nausea/Vomiting
- Pain
- Fever
- Sepsis
- Hypotension
- Mech. Ventilation

Routine Fluid Needs Paediatric (Baseline)

Include term neonate

Fluid Requirement Age based	Fluid Requirements (per kg/hour)	Fluid Requirements (per kg/24 h)
< 1 y = 120 ml/kg/24 h	< 5 kg = 6 ml/kg/h	1-20 kg = 100 ml/kg/24h
1-2 y = 100 ml/kg/24 h	5-10 kg = 5 ml/kg/h	11-20 kg = 1000 ml + 50 ml/kg/per each kg over 10 kg in 24 h
2-3 y = 85 ml/kg/24h	11-15 kg = 4 ml/kg/h	> 20 kg = 1500 ml + 20 ml/kg/per each kg over 20 kg in 24 h up to 40 kg
> 3 y = 70 ml/kg/24h	16-35 kg = 2-3 ml/kg/h	> 40 kg 30-50 ml/kg/24 h
	> 36 kg = 1-2 ml/kg/h	

Neonate 1,2 to 2 kg	Neonate 2 to 2,5 kg	Neonate > 2,5 kg
Day 1 = 20 ml/kg/24h	Day 1 = 25 ml/kg/24 h	Day 1 = 30 ml/kg/24 h
Increase 20 ml/kg/day Max 160 ml	Increase 25 ml/kg/day max 150 ml	Increase 30 ml/kg/day Max 150 ml

Routine Maintenance Paediatric

- Electrolyte requirements for 24 h (mEq/kg)
- Meet Caloric Needs

Age	Na	Cl	K	Ca	Mg	Po
Neonate	2-5	2-5	1-2	2-4	0.3-0.5	1-2
Infant/child	2-5	2-5	2-4	0.5-4	0.3-0.5	0.5-3
Adolescent	1-2	1-2	1-2	10-20	10-30	1-2

Solutions: Neonatalyte, ½ DD

Replacement and Redistribution Issues

Existing Fluid-electrolyte deficits or excess?	Ongoing abnormal Loses?	Redistribution – complex issues?
Check & Estimate: 1. Dehydration 2. Fluid overload 3. Degree of deficit-excess for: • Na & Cl • K • Ca, Mg, PO4 • Acid-base status	Check & Estimate amount of: • Vomiting-NG output • Biliary drainage • SB Stomas • Diarrhoeas • Fistula • Polyuria • Fever-sweating	Check: • Gross oedema • Severe sepsis • Hyper-hyponatraemia • Renal-liver-cardiac failure • Post op fluid retention/mal distribution • Malnourished – refeeding syndrome • Ask for help • Estimate requirements

Composition of some Body Fluids Loses (70 kg patient)

Fluid	Na	K	Cl	HCO3	Volume/day
Saliva	60 mmol/L	20 mmol/L	16 mmol/L	50 mmol/L	± 1500 ml
Gastric	60 mmol/L	10 mmol/L	90 mmol/L		± 1500 ml
Pancreas	140 mmol/L	5 mmol/L	75 mmol/L	70 mmol/L	± 2000 ml
Bile	145 mmol/L	5 mmol/L	100 mmol/L	50 mmol/L	± 750 ml
Small Bowel	120 mmol/L	5 mmol/L	105 mmol/L	20 mmol/L	> 5 L produced

Results of Electrolyte Loses in Surgery

Loses	Electrolytes Changes	Results
Gastric (aspirate, fistula, vomiting)	Low Na, Low Cl, Low K, high HCO3	Hypochloraemic metabolic alkalosis
Pancreatic Fistula	Low Na, Low K, Low HCO3, Normal Cl	Hyponatraemic, hypokalaemic metabolic acidosis
SB ECF	Low Na, Cl, K, HCO3	Hyponatraemic, hypokalaemic metabolic acidosis
Biliary Fistula	Low Na, Cl, K, Normal HCO3	Alkalosis may occur
Diarrhoeas (water loss)	High Na, Cl, HCO3 Low K	Hyperchloraemic metabolic Acidosis (non anion GAP)

Replacement: Adult

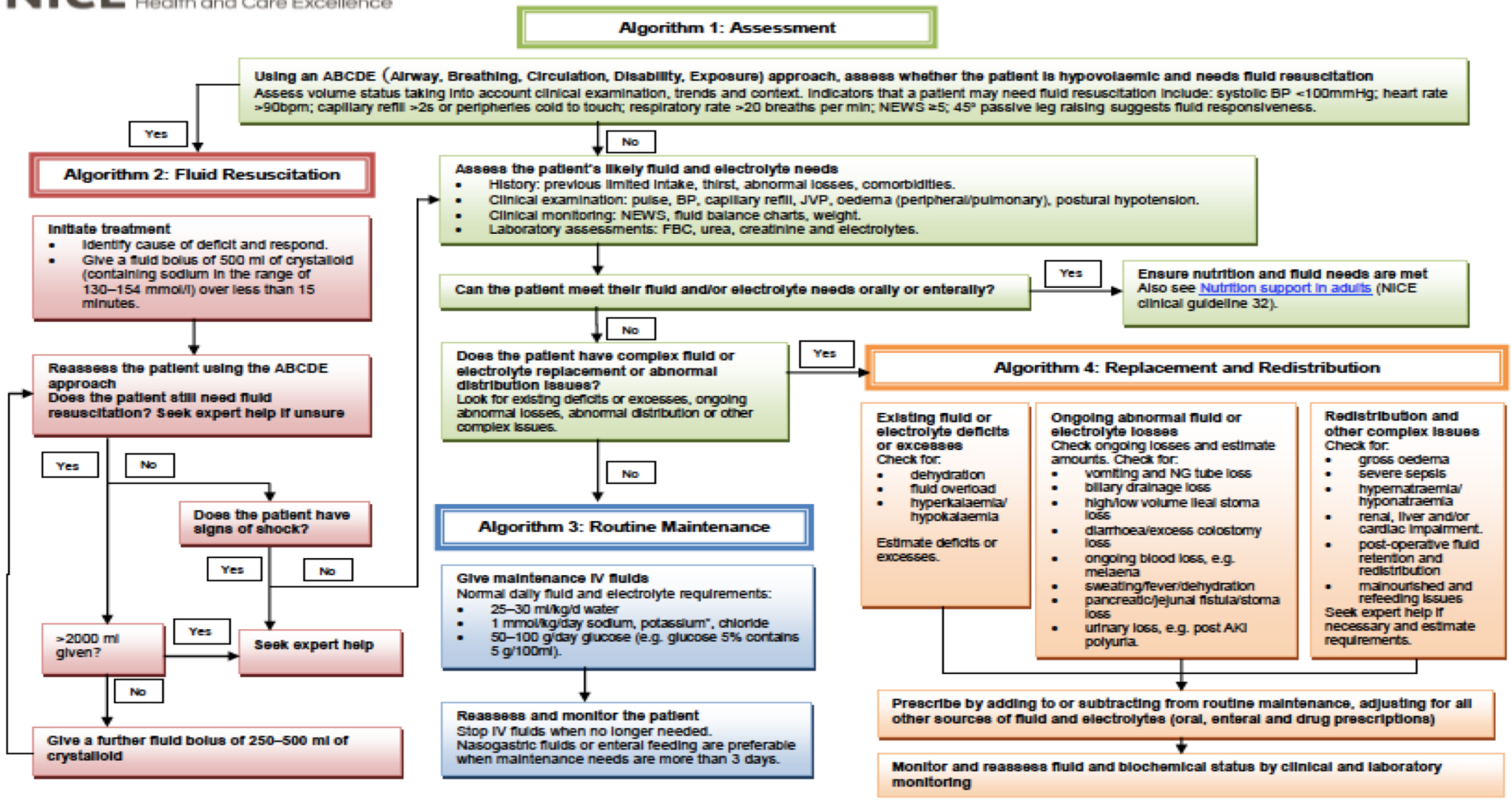
- **Deficit added or excess subtracted from baseline daily needs (Maintenance)**
- Usually done by monitoring 4-6 hourly loses of water and then using Na containing crystalloid resuscitation fluid (Ringer, Plasmalyte B) to administer equal volume (the 1:1 formula)
  - i.e.: ECF loosing 450 ml every 6 hours, then 450 ml of Ringer Lactate should be added to maintenance every 6 hours to keep water balance (i.e. 2500 ml Maintenance + 450 ml x 4 (1800 ml) = 4300 ml in 24 h)
- Monitor acid-base balance for early detection and correction of acidosis (hypoperfusion, HCO_3 loses) or alkalosis (hypochloraemia)

Replacement: Adult

- Electrolytes are monitored daily (include CMP) and replaced PRN
- Do not add KCL to IV maintenance fluids: dangerous practice!!
- Replace K using infusions over 3-4 h and re-assess (Oral K is an option is patient able to use oral-enteral route)
- Remember Calories, Fat and Protein requirements (unless present in maintenance solutions)
- Add Vitamins and trace elements (unless present in maintenance solutions)

NICE National Institute for Health and Care Excellence

Algorithms for IV fluid therapy in adults



*Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period).

Potassium should not be added to intravenous fluid bags as this is dangerous.

'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013. Last update December 2016)

Deleterious effects of inappropriate fluid use

Increased need for Damage Control Surgery
Increased incidence of Abdominal Compartment Syndrome
Coagulopathy, increase blood loss
MOF (AKI, ARDS, Gut)
Increased need for blood transfusions
Increased risk of anastomotic failure
Increased LOS in ICU and hospital, increased costs
Large volume usage predictor of mortality

INFLAMMATION

Synthetic Colloids

S6
CHEST, CRYSTMAS
CRYSTAL, VISEP Trials

Starches – Gelatins - Dextran (no longer used)

- Known to increase rate of MOF, especially septic patients
- Coagulopathy and increase need for blood transfusions
- Data not validated in trauma cases (extrapolated results)
- “Unclear” relation between Colloids and Mortality in Critically Ill patients
- Limited data in bleeding trauma patients (increase mortality)

FIRST study - HES vs Saline in Trauma: no differences in mortality, improved Lactate clearance in penetrating trauma, criticized due to design flaws (James MF et al BMJ 2011)

Albumin Controversies

Reasons in Favor of Use as routine replacement in Critically Illness

Natural Protein responsible for Oncotic pressure (80%) Regulates volaemia
Scavenger effect (free O2 radicals) (Cysteine residue - thiol)
Anti-Nitric Oxide (NOS): reduce vasodilatory effect of NOS (Cysteine residue - thiol)
Buffer effect in the extra-vascular space (Histidine Imidazole residues)
Transport protein (Domains I-II) Low levels may result in toxicity and poor drug efficacy
Low levels are associated with increased mortality, complications and LOS in ICU-Hospital

HALLMARKS OF CRITICAL ILLNESS PROCESSES: SYSTEMIC INFLAMMATION, HIGH OXIDATIVE STRESS (VASODILATION) AND METABOLIC ACIDOSIS (LACTATE)

Albumin Controversies

Reasons Against the use as routine replacement in Critically Illness

Natural protein: Allergic reactions
Normal response in critical illness is to reduce production (preservation of proteins) Non pathological
Association with increased mortality is an expression of disease severity rather than Albumin DIRECT effect
Oncotic effect defeated by the Endotheliopathy of critical illness (shedding Glycocalyx, Leaky capillaries)
Albumin will leak to interstitial space and stay there due to impaired lymphatic clearance (↑oncotic pressure IS, worsening oedema, MOF)

Albumin for Routine Replacement

- Evidence: Seems to be safe
- No influence in survival compared with crystalloid (NaCl) (SAFE study ALBIOS trial)
- Not to be used in TBI with GCS < 8 (increased mortality first week – SAFE study post hoc analysis, linked to increased ICP-oedema)

SAFE study Finfer et al NEJM 2004; ALBIOS Trial Caironi et al NEJM 2014

Albumin for Resuscitation: Sepsis/Septic Shock

- Theoretically YES = anti-oxidant, anti NOS and Glycocalyx stabilizer
- But marginal benefit only seen if HD stability is present (ALBIOS)
- If endothelial damage is present (ongoing) it may worsen oedema and organ dysfunction
- Slight influence in survival (SAFE post hoc analysis)
- HD effect is not clinically significant (ALBIOS)
- Safe intervention but not effective to reduce mortality (Patel et al BJM 2014 Metanalysis)

Albumin in ARDS

- In combination with Furosemide seems to improve oxygenation in HD normal ARDS patients with hypoproteinemia
- NO survival benefit is achieved

Albumin in Burns

- Safe to use
- Anti-oxidant and oncotic effects
- No differences in outcome irrespective of albumin levels (*Melnyshyn et al 2013*)
- No improvement of organ function when 4% albumin added to Ringer Lactate (*ALBUR - Cooper et al 2006*)
- Albumin use does not: Improve survival, LOS in ICU or healing rate (*Mohammadi et al 2014 RCT*)

Other potential uses of Albumin

- Glycocalyx stabilizer (Albumin constitutes 70% of glycocalyx), may be used to stabilize endothelial surface (Counter argument: ongoing inflammation results in persistent endothelial damage)
- Fat scavenger in FES and TPN lipid overload (Free-fatty Acids bind to Albumin, especially Oleic acid, know to cause lung damage)

References

- *Caironi P et al. The clinical use of albumin: the point of view of a specialist in intensive care Blood Transfusion 2009;7:259-267*
- *Cantle Pm et al Balanced resuscitation in trauma management Surg Clin N Am 2017;97:999-1014*
- *Kalantari K et al (Review) Assessment of intravascular status and fluid responsiveness in critically ill patients Kidney International 2013;83:1017-28*
- *National Institute for Health Care Excellence (NICE) Clinical Guidelines 2013 (update 2017)*
- *SAFE study Finfer et al NEJM 2004; ALBIOS Trial Caironi et al NEJM 2014*

Thank you!

Functions of Cells and Human Body
Multimedia textbook

Introduction
Textbook
I. Cell Structure
II. Transformation of Substances and Energy in the Cell
III. Cell and Tissue Signalization
IV. Locomotive System
V. Blood and Immune System
VI. Respiratory System
VII. Kidneys, Water and Ion Balance and Acid-Base Balance
1. Functional Morphology of the Kidneys
2. Renal Blood Circulation
3. Urine Formation
4. Endocrine Functions of the Kidneys
5. Role of the Kidneys in the Intermediary Metabolism
6. Metabolism of Water and Ions
7. Acid-Base Balance
Test Yourself
Case report
VIII. Reproductive Systems
IX. Gastrointestinal Tract
X. Heart and Blood Circulation
XI. Regulatory mechanisms 1: Endocrine regulation
XII. Regulatory mechanisms 2: Nervous regulation
XIII. Senses
XIV. Videos
XV. iBook textbook
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6. Metabolism of Water and Ions

Content:

Introduction to metabolism of water and minerals

The internal environment can be defined as **the composition of the fluid that bathes the cells**. Maintaining a **constancy in the internal environment of the human body** – its constant composition, is absolutely essential. This is one of the **vital functions** such as breathing or blood circulation.

The basic components of the internal environment include:

1) Constant volume

2) Constant tonicity and **constant ionic composition**

3) Constant pH

In this chapter we will further pursue the first two points. The issue of maintaining constant pH will be discussed in detail in subchapter about acid-base balance.

Body water and its distribution, osmolarity

Body fluids

All the water in the human body is summarized under the concept of **total body water** (**TBW**). It constitutes **55-60 % of body weight** in adults. Women have a **lower TBW than men** because they have a **higher proportion of body fat** (the same rule applies to people who are **overweight** or **obese**). **Young children** and **pregnant women** have an **increased proportion of TBW**, but, with old age, the proportion of water in human body **decreases** (we can overstate and say, that as we age, our bodies gradually dry up).

Total body water is divided into two basic groups – **intracellular** and **extracellular fluid**.

Intracellular fluid (**ICF**) contributes **2/3 of adult TBW** while extracellular fluid **(ECF)** contributes the remaining **1/3 TBW**. In **neonates** the distribution is **reversed** – ICF is 1/3 TBW, ECF 2/3 TBW.

Extracellular fluid is further divided into the **liquid stored in the arteries** – **intravascular fluid** (**IVF**, plasma + lymph), contributing **1/4 ECF**, and the **interstitial fluid (tissue fluid)** contributing **3/4 ECF**.

Sometimes, the above is expressed as **a percentage of body weight** (% b. w.):

TBW (60 % t. h.) = ICF (40 % t. h.) + ECF (20 % t. h.)

ECF (20 % t. h.) = ISF (15 % t. h.) + IVF (5 % t. h.)

Certain fluids are held in a so called **third space** or preformed cavities. These include:

1) Cerebrospinal fluid

2) Liquid secreted to the gastrointestinal tract (digestive juices, …)

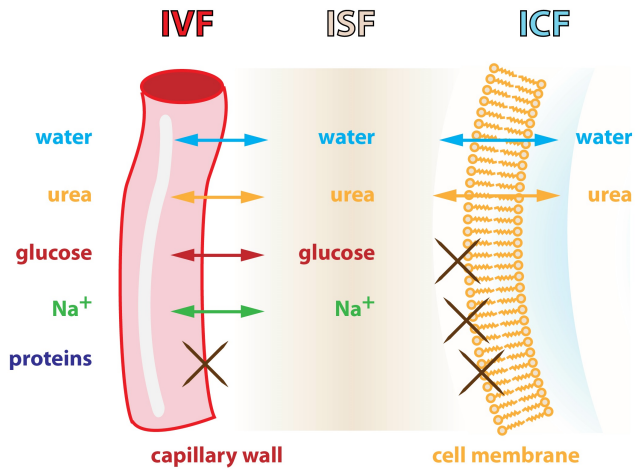
3) Synovial fluid

4) Fluid in the pleural, peritoneal and the pericardial cavity

Laws of water distribution and osmolarity

The water in the human body is moved by **osmosis** (most bodily barriers are **semipermeable**). The water content in the various compartments of the body is determined by **the content of osmotically active particles – osmolarity**. If deflection in osmolarity occurs anywhere in the body, an induced movement of water molecules through a semipermeable membrane occurs, in order to compensate for this deflection.

Figure captures three major compartments of the human body and the movement of individual substances across their borders.



Plasma osmolarity

Osmolarity is defined as the **number of osmotically active particles in a liter** – [mosm/l] = [mmol/l]. The physiological range is considered to be **280-295 mmol/l**, with a most of the particles being **low molecular weight substances** – **ions, nutrients** and **metabolites**. Consequently we obtain an approximate idea of the osmolarity by a simple sum of concentrations of routinely measured substances -we obtain the so-called **calculated osmolarity** :

Calculated osmolarity = 2 [Na^+] + [glucose] + [urea]

By cross-comparison of measured and calculated osmolarity values we obtain the so-called **osmotic gap** (**OG**):

Osmotic gap = measured osmolarity – calculated osmolarity

OG is comprised of all substances which we do not count when calculating the calculated osmolarity – its normal range is **4-12 mmol**.

In many pathological conditions, we find OG increasing above normal physiological values. Two primary causes of this are:

1) Accumulation of foreign substances to the human body – For example, during a **poisoning** (e.g., ethanol, methanol, ethylene glycol)

2) Accumulation of substances, **which are commonly found in the body, but their metabolism is altered** – e.g., excessive catabolism in diabetes mellitus type 1 (overproduction of ketone bodies etc.).

Regulation of osmolarity

Fluctuation in body osmolarity is normally very low – only **± 1-2 %**. The osmolarity of body fluids is regulated by the **content of free water in the body**. The main regulatory mechanisms are **simple feedback** via **antidiuretic hormone (ADH, vasopressin)** and thirst inducement.

Within **lateral hypothalamus** is an area we call the **center of thirst**. Neurons in this structure are able to monitor the **osmolarity of the surrounding fluid**. If surrounded by a hyperosmotic environment, shrinkage occurs in these cells (diffusion of water from the intracellular compartment into the extracellular hyperosmotic compartment), leading to a change in their activity, and ultimately inducing a strong **feeling of thirst**.

In the **supraoptic area** are similar neurons with osmoreception abilities. Those in hyperosmotic fluid increase its activity and through projections passing through the infundibulum into the **neurohypophysis** (posterior lobe of the pituitary gland) release **antidiuretic hormone** (ADH or vasopressin) from axons into adjacent capillaries. ADH

subsequently flows via circulation to the kidneys, where it binds to its receptors on the **cell membrane of cells in distal tubuli** and **collecting ducts of the kidneys**. ADH causes **increased permeability** of the cells by **water**, which causes the so-called **facultative water resorption** and formation of **more concentrated urine**. These cells carry **V2 membrane receptors for ADH**, which get activated by ligand (ADH) binding that leads to activation of adenylate cyclase – cAMP formation – incorporation of **aquaporins-2** (channels for water) to the apical membranes of cells. Aquaporins allow the passage of water by osmotic gradient from the **lumen of the nephron into the hyperosmolar environment of the kidney medulla**, where the water is drained by blood vessels. The result is an **increase in urine osmolarity** (the water is drawn from it, the solute is not) and a **decrease in body osmolarity** (for free water retention in the body). **ADH simultaneously increases cell membrane permeability** in cells of the collecting ducts for urea through increased expression transporters for urea (e.g. UT-A), which facilitate the reabsorption of urea into the interstitium medulla . This further enhances the absorption of water.

Antidiuretic hormone shows further effects in the human body, which we will not deal with at this point – they are discussed in other subchapters.

In addition to the above-described endocrine regulation an increase in body osmolarity affects a person's behavior by **inducing thirst** → searching for and drinking fluids.

Disorders of antidiuretic hormone secretion

In case of an insufficient effect of ADH (insufficient secretion of hormone or absence of its receptors) appears **excessive diuresis** (polyuria – up to 30 liters per day) and **excessive thirst** (polydipsia). This disease is called diabetes insipidus.

The opposite condition is a syndrome of inappropriate secretion of ADH – SIADH (Syndrome of Inappropriate ADH secretion, Schwartz-Bartter syndrome), which leads to excessive secretion of ADH, which does not reflect the current state of osmolality. It leads to **water retention**, **hypoosmolarity** and **dilutional hyponatremia** (relative shortage of Na^+ – usual amount is dissolved in large quantities of water). In more severe conditions **brain damage** develops due to the **edema**. This is due to intracranial pathologic processes or tumors producing ectopic ADH.

Clinical significance of plasma osmolarity

In clinical practice we frequently encounter osmolarity complications. For example, with each infusion, the doctor must take into account that the infusion has some osmolarity and that it will not harm the patient as a result. We always have to respect the tonicity of the infused solutions. By **comparing the osmolarity of administered solutions with plasma osmolarity** we can categorize the following solutions:

1) Isotonic solutions

Isotonic solutions have a **similar osmolarity as plasma**. These are the most frequently encountered in practice.:

a) Normal saline (NS) – **0,9% NaCl**, 154 mmol/l Na^+ and Cl^-

b) 5% glucose – free water remains after glucose metabolism – **de facto hypotonic solution**

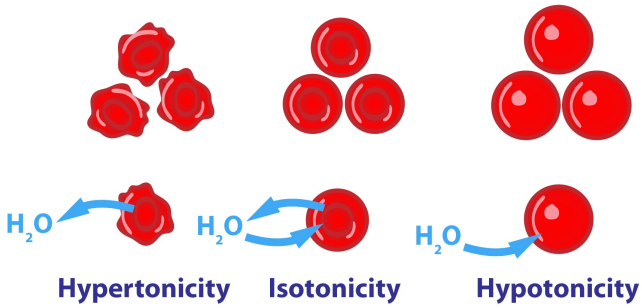
c) Ringer's and Hartmann's solution – **ionic composition similar to plasma**

2) Hypotonic solution

Excessive administration of hypotonic solution may cause **hemolysis** (destruction of red blood cells) and **brain edema**. Examples of hypotonic solutions: NS 1/2, R 2/3, H 2/3.

3) Hypertonic solutions

Hypertonic solutions can irritate the wall of blood vessels and cause damage to the CNS. Examples of hypertonic solutions: G 10%, G 20%, G 40%, NaCl 10%.



Changes in osmolarity are a particular threat to the brain. The **rapid decline in ECF osmolarity** can result in **brain edema**. A **rapid rise in ECF osmolarity** may in turn lead to the **pontine myelinolysis**.

Regulation of extracellular fluid volume and sodium metabolism

The **volume of the circulating fluid** is essential for **maintaining blood pressure**. Hemodynamic parameters conversely help to regulate the content of Na^+ in the body.

Sodium cation – Na^+

Sodium cation is the **primary cation of extracellular fluid**. Its concentration in ECF is **135-145 mmol/l** , the concentration in intracellular fluid is much lower – about 10 mmol/l. Sodium cation is along with **chloride cation** responsible for **80 % of the ECF osmolarity** – it binds the most water of all ions (therefore retention of Na^+ causes water retention). The **content of Na^+** thus **determines the content of water in the ECF** and hence in **IVF**. Volume of intravascular fluid is critical for the regulation of blood pressure and cardiac output.

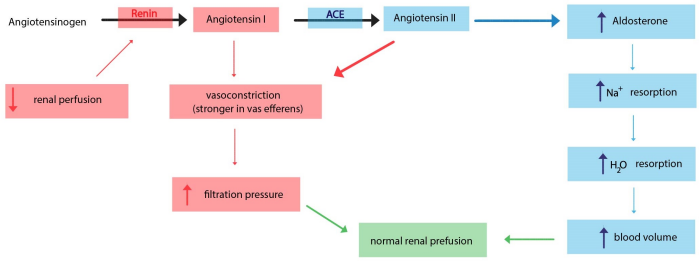
We ingest Na^+ primarily in the form of **salts**. The recommended daily dose is approximately **2.4 g** (70 mmol), which equals to **6 g NaCl**. However in reality, the salt intake in developed countries is much higher, which increases the risk of **developing hypertension**. Na^+ is excreted primarily through the **kidneys** (U – Na = 50-200 mmol/l) and **sweat** (sweat is hypotonic fluid). The kidneys have a high ability to secrete Na^+.

Regulation of Na^+ concentration in the body

Na^+ content in the body is regulated by two main systems – **the renin-angiotensin-aldosterone system** and **the system of natriuretic peptides.**

Regulation via the renin-angiotensin-aldosterone system (RAAS)

In the **case of insufficient blood flow** to the kidneys (e.g., decrease in blood volume) cells of the **renal juxtaglomerular apparatus** begin the synthesis of protein **renin**. Renin is an enzyme, which catalyzes the conversion of plasmatic **angiotensinogen to angiotensin I**. Angiotensin I is then converted by **angiotensin converting enzyme** to **angiotensin II**, which stimulates aldosterone synthesis and causes vasoconstriction. Aldosterone production is also stimulated by **increased levels of serum potassium**.



The main effects of aldosterone (mineralocorticoids) are:

1) Retains Na^+ and water in the body – they strengthen Na^+ absorption in the distal tubuli

2) Increases blood pressure by increasing in extracellular fluid volume (intravascular fluid predominantly) – related to point 1)

3) Increases urine excretion of K^+ a H^+ in distal tubuli

Regulation by the natriuretic peptides

At present we know of several natriuretic peptides. Two of them are considered to be principal – **ANP** (**atrial natriuretic peptide**) and **BNP** (**brain natriuretic peptide**). Both have significant **vasodilating** effects, **increase natriuresis** (they inhibit reabsorption of Na^+ in distal tubuli – increase in Na^+ losses to the urine) and **diuresis** and **reduce sympathetic activity**. Quite unusual is the fact that both are secreted by cells of the **heart** – the heart is therefore an endocrine organ.

ANP is secreted by cardiac **atrial cardiomyocytes**, and the stimulus for secretion is **increased wall stress** in the atria (e.g., **increased venous return** – causes expansion of the atria). BNP was first described in porcine brain (the reason for the designation). In humans , however, it is secreted primarily by **cardiomyocytes in heart ventricles** – the signal is increased **tension in the wall** of the ventricle or ventricular dilatation. Natriuretic peptides thus mediate the body's response to **excess Na^+ and increased blood volume** – their significant secretion occurs in response **volume overload of the heart**.

Clinical correlation:

In clinical practice, levels of natriuretic peptides, predominantly the N-terminal fragment of **proBNP (NT – proBNP)**, are measured to **rule out** heart failure in people who present with sudden difficulty in breathing or to determine the **prognosis of patients with known heart failure**.

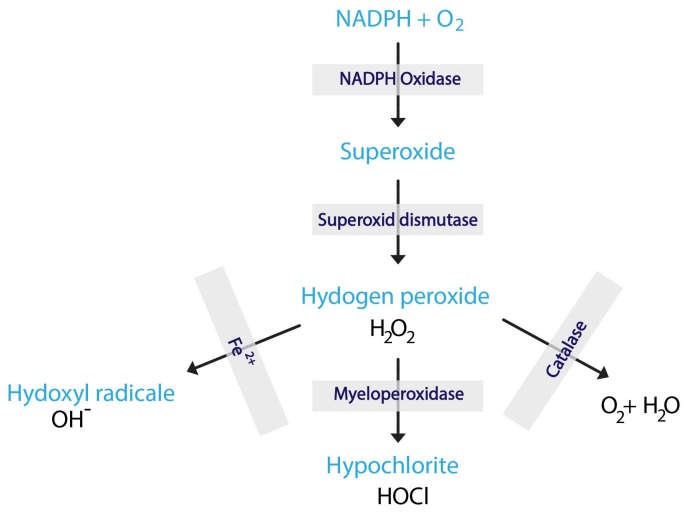
Reserves of Na^+ in the body can be assessed by **clinical examination**. Decreased volume of ECF can result in **dry mucous membranes, orthostatic hypotension and tachycardia** (potentially shock). On the contrary increased volume of ECF indicate **edema** and **lung crackles**. Laboratory tests for Na^+ reserves are used secondarily (S -Na^+).

Na^+ losses can occur in several ways – through **urine**, **sweat** or through the **GIT**. Some causes of loss through urine are **administration of diuretics, osmotic diuresis** (hyperglycaemia in DM), polyuric phase of renal failure, **insufficient production of aldosterone**, insensitivity of the distal of distal tubule cells in kidney to aldosterone. Losses through GIT occur during **vomiting, diarrhea** or through fistula and drains. Significant quantities of Na^+ may also leave the body due to **excessive sweating**.

Metabolism of other ions

Chloride anion – Cl^-

Chloride anion is the **main anion of extracellular fluid**. Its concentration in ECF is **97-108 mmol/l** . The concentration in intracellular fluid is much lower – **3-10 mmol/l**. The chloride anion accompanies the sodium cation, and together they account for **80 % of the osmolarity of the ECF**. Cl^- is of great importance for **maintaining acid-base balance – exchange for HCO_3^-** (if losses of Cl^- occur, body replaces them by the bicarbonates, in the retention of Cl- bicarbonate levels decrease). Yet HCl is a much stronger acid than H_2CO_3. Therefore, with Cl- losses metabolic alkalosis occurs and, vice versa, the retention of Cl^- results in metabolic acidosis. For details, see subchapter about acid-base balance. Our immune cells can utilize the **H_2O_2-myeloperoxidase-Cl^- system** to aid in the destruction **destruction of phagocytosed microorganisms**.



Chlorides are primarily ingested in the form of **salts** – therefore they are received with an **equimolar amount of Na^+**. Likewise, chlorides are excreted along with Na^+ (kidneys reabsorb them along with Na^+).

Hypochloremia can result from the following conditions: **vomiting,** collection of gastric juice or during **excessive sweating**.

Potassium cation – K^+

Potassium cation is one of the **main intracellular cations** as is the magnesium cation. 98 % of K^+ is in the intracellular fluid – concentration of **~ 155 mmol/l** , only 2 % remains in the ECF – concentration of **3.8 to 5.2 mmol/l**. From this distribution it is apparent that the plasma levels provide us very limited information about the state of body reserves of this ion. A change in the S-K^+ occurs only when the amount of K^+ in the body is above 100 mmol. **The shifts in potassium levels** show predominantly in its changed **distribution** – doctor should monitor urine and waste balance.

Every day we **ingest** about 100 mmol K^+ , the main source is **vegetable diet** (fruits and vegetables). **Losses** of K^+ occur principally through excretion in **urine** – U-K^+ = **~** 45 mmol/l and **faeces** – 12-18 mmol/day. K^+ excretion through the kidneys depends on its intake and the levels of regulatory hormones – **mineralocorticoids** (mainly **aldosterone**). The majority of K^+ is absorbed in the proximal tubule. Less than 10% of K^+ gets to **distal tubuli** – here is the primary spot of regulation – Na^+ is reabsorbed in exchange for K^+ and H^+ (excretion of K^+ is supported by mineralocorticoids – aldosterone). By comparing serum and urine concentrations, it is apparent that the kidneys are **powerful at retaining Na^+** and, conversely, at **eliminating K^+**: S-Na^+ = 140 mmol/l , S-K^+ = 4 mmol/l, U-Na^+ = 110 mmol/l and U-K^+ = 45 mmol/l → serum ratio of Na^+/K^+ 32:1, urine 2-3:1.

Distribution of K^+ between intracellular and extracellular fluid

Intra-and extracellular distribution of K^+ is influenced, for example, by:

1) Na^+/K^+-ATPase function

2) pH

3) Cellular catabolism and anabolism

4) Insulin and glucose

1) Na^+/K^+-ATPase function

Na^+/K^+-ATPase functions as an **antiport** and **for ATP consumption transmits three Na^+ cations outwardly from the cell in exchange for two K^+ cations directed to the cell.** (For more information, see Chapter 2). When there is inadequate energy production in the cells, the transfer of ions through the Na^+/K^+-ATPase is slowed down – K^+ remains in the ECF and the local level increases while the concentration in the ICF drops.

2) pH

During **acidosis** cells operate as “gigantic buffers” – they take in H^+. But since they took in a cation, a different cation has to be released into the ECF – K^+ is leaving the cells and their **EC concentration increases**. The whole process is reversed by alkalosis. For more information, see subchapter about acid-base balance.

3) Cellular catabolism and anabolism

During **catabolism cleavage of intracellular proteins occurs**, thus releasing previously bound potassium cations which subsequently pass into the **extracellular fluid** – potassium levels increase. The opposite process takes place during anabolism. Particularly threatening is rapid anabolism after prolonged catabolism, which can lead to severe hypokalemia.

4) Insulin and glucose

Insulin conditioned entry of glucose into cells is accompanied by a transition of K^+ into cells. This is often used in the acute treatment of hyperkalemia when a glucose infusion with insulin is administered.

Summary of regulation of K^+ in the body

1) Regulation of the distribution of K^+ between ECF and ICF – is responsible for acute shifts in S-K^+:

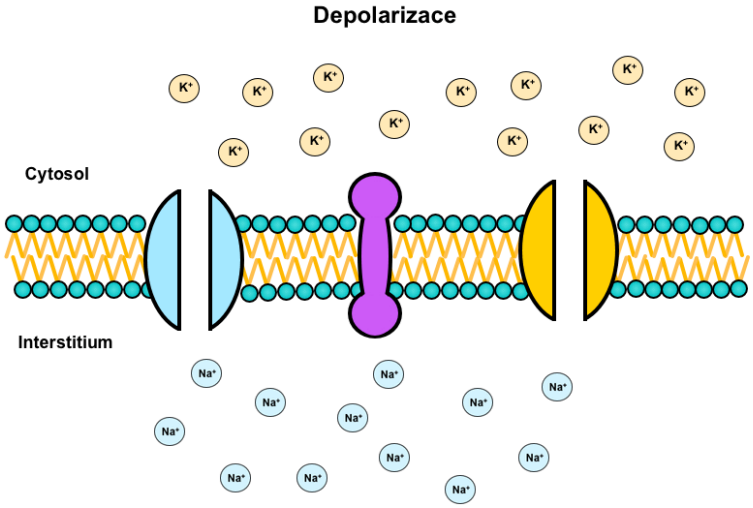
a) Energetic state of cells, Na^+/K^+-ATPase

b) pH: alkalosis decreases S-K^+, acidosis does the contrary

2) Regulation of the K^+ excretion in distal kidney tubuli – mineralocorticoids (aldosterone) increase local **K^+ excretion**

The importance of potassium cation

Physiological distribution of cations on the membrane (Na^+ mainly extracellularly and K^+ predominantly intracellular) is necessary for maintaining proper cell function (neuromuscular irritability, excitability of cells of the conduction system of heart, etc). The **gradient** of these ions between the ICF and ECF **affects membrane potential**. The correct ratio of the two ions is ensured by **active participation of Na^+/K^+-ATPase**.



Changes in potassium levels – hyperkalemia and hypokalemia

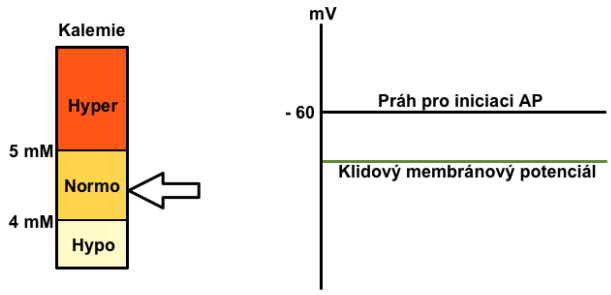
Hyperkalemia

Hyperkalemia, or increased plasmatic K^+, can have many causes:

1) Renal failure leads **to inadequate secretion of K^+** by the kidneys

2) The failure of the adrenal cortex leads to defective production and secretion of aldosterone, a hormone that lowers serum potassium levels (Addison's disease).

Symptoms of hyperkalemia include **muscle weakness and abnormal ECG findings** (see below). S-K^+ values over 7,0 mmol/l are indications for **hemodialysis**. Higher values can be fatal, they can cause **sudden cardiac arrest** resulting from **ventricular fibrillation** (sometimes occurs even at lower values).



Hypokalemia

Hypokalemia, or decreased plasmatic K^+, can have many causes:

1) Hyperaldosteronism or long-term treatment with glucocorticoids which in high quantities have similar effects as mineralocorticoids (aldosterone)

2) Diuretic overdose (furosemide)

3) GIT fluid losses – diarrhea

Symptoms of hyperkalemia include **muscle weakness** (up to paralytic ileus) and **heart rhythm disorders**.

How are potassium level shifts reflected on the ECG?

A typical finding in hyperkalemia is shortened repolarization, QT shortening, with a narrow peaked T. On the contrary, in hypokalemia the typical finding is prolongation of repolarization, prolonged QT, flat T.

Magnesium cation – Mg^{2+}

Magnesium cation is **second major intracellular cation**. Its concentration in the extracellular fluid is 0.7-1 mmol/l. Magnesium has the following **roles** in the body:

1) Structural function in bones (2/3 Mg in the body)

2) Cofactor of 300 enzymes

3) Reduces neuromuscular excitability

Our average daily intake of Mg^{2+} are just units of mmol (legumes, grains, vegetables, milk).

Hypomagnesemia is manifested by **muscle weakness**, **cramps**, gastrointestinal problems and nonspecific ECG changes. It is common in alcoholics.

In the treatment of certain diseases, such as **preeclampsia** and other **seizure disorders**, we use **induction of hypermagnesemia as a therapy** – iatrogenic hypermagnesemia (infusion of 20% MgSO4).

Calcium and phosphate metabolism

Calcium cation – Ca^{2+}

Calcium forms about **1.5 % of total body weight**. The level of calcium cations in the extracellular fluid (**2.25-2.75 mmol/l**), is about **four times higher** than its intracellular concentration. **99 % of Ca^{2+} resides in the bones in the form of hydroxyapatite**, where it serves as a mechanical support and prompt supply of Ca^{2+}. **In plasma** we **differentiate two basic fractions** of Ca^{2+} – **bound** and **free** – see Chapter 5. There is a certain balance between its quantity in bone tissue and its plasma concentrations.

Importance of Ca^{2+}

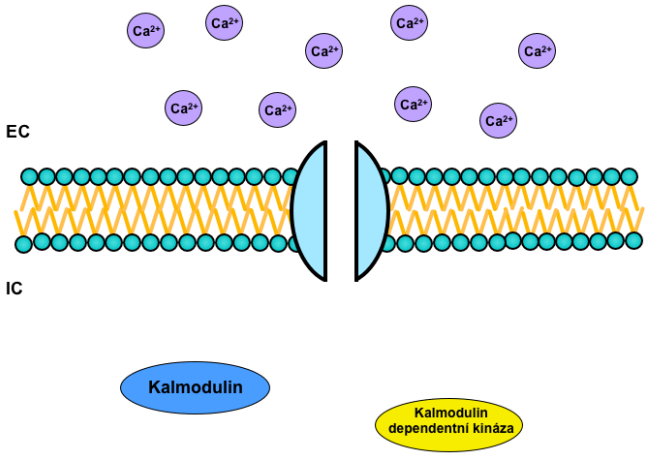
The role of the calcium cation is **stabilization of membranes of excitable tissues** (its absence leads to cramps), contribution to **muscle contraction and coagulation – blood clotting** (calcium cation is an activator of coagulation factors, whose formation is dependent on vitamin K – f II, VII, IX, X, protein C and S, and Ca^{2+} itself is a **factor IV**), and it is necessary for **lactation**. Calcium is also part of the inorganic **bone matrix (hydroxyapatite**). It is also structural component of the **teeth**.

Intracellular Ca^{2+}

Ca^{2+} has the **largest concentration gradient between extracellular and intracellular environments** of all ions. In the cytosol there is a very low physiological concentration of Ca^{2+} – **10^{-7}-10^{-8} mmol/l**. This gradient is maintained by **secondary active transport of Ca^{2+} for 3 Na^{+}** and by **active transport of Ca^{2+}-ATPase**. Ca^{2+} enters the cell through the **calcium channels**.

Roles of Ca^{2+} in the cell

Calcium ions work as a second messenger in the cell. Many of its effects are mediated through **calmodulin**, a major intracellular Ca^{2+}**-binding protein**.



Increase in the intracellular Ca^{2+} concentration affects many important cellular processes:

1) The release of neurotransmitters at nerve synapses

2) Regulation of energy metabolism – activates protein kinase C, glycogenolysis, etc.

3) Regulation of muscle contraction

On the other hand, prolonged increase in intracellular Ca^{2+} concentration can lead to **cell death**.

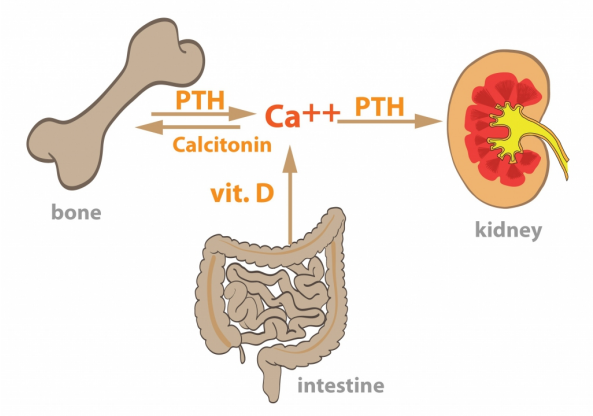
Reabsorption and excretion of the calcium cation

The recommended daily dose of calcium for adults is approximately 1 g. The main sources are milk, dairy products and eggs. Its resorption from GIT is physiologically around 25-40 %, located primarily in the **duodenum** and **jejunum**. A specific transport protein, **calbindin**, is found on the apical membrane of enterocytes. On the basolateral side calcium is actively transported against the concentration gradient into the ECF.

Excretion of calcium is through **urine** and **faeces**. Ca^{2+} bound to plasma does not pass to the primary urine. Reabsorption takes place in proximal tubule and the ascending part of the HK.

Regulation of Ca^{2+} a phosphate content in the body

Three hormones in the human body play a key role in Ca^{2+} and phosphate content regulation – **parathyroid hormone, calcitriol** and **calcitonin**.



1,25-dihydroxycholecalciferol – calcitriol (vitamin D derivative)

Vitamin D, particularly in the form of vitamin D3, is received from nutrition, but the body can also synthesize it from its **provitamin 7-dehydrocholesterol**. It is located in the cells of the epidermis, and **photolysis with UV light** forms vitamin D3. The **liver can hydroxylate** both dietary and synthesized vitamin D3 **at position 25** and forms **25-hydroxycholecalciferol**. If required by the body, this may be further **hydroxylated at position 1** (the result is effective

1,25-dihydroxycholecalciferol, or **calcitriol**) or at position 24 (to an **inactive metabolite**). Enzymes catalyzing 1-hydroxylation are present in the **kidney**, bones and placenta.

Calcitriol **stimulates protein synthesis in the small intestine** allowing **absorption of Ca^{2+} and phosphates**. This ensures the **availability of Ca^{2+}** and **phosphates for bone growth**. It simultaneously **activates osteoblasts for collagen synthesis**.

Hypovitaminosis leads to **defective bone mineralization**, which causes **rickets** in children, characterized by deformation of the skull, spine, chest, and long bones. In adults, bone decalcification manifests by their softening – this is known as **osteomalacia**. Causes of vitamin D deficiency deficiency are not only its **insufficient intake** but also a lack of exposure to sunlight or **kidney disease**.

Hypervitaminosis D manifests by thirst, diarrhea and vomiting, itching of the skin and **deposition of calcium salts** in soft tissues (e.g., blood vessel walls or in the kidneys).

For more information about vitamin D and calcitriol see Chapter 9.

Parathormone

Parathormone is a peptide hormone produced by the **parathyroid glands**. **It stimulates degradation** (resorption) **of bones by increasing osteoclast activity** (stimulates the transformation of monocytes to osteoclasts). The result is an **increased release of Ca^{2+} and phosphate from bones**. PTH **affects kidneys – inhibits Ca^{2+} excretion** (increased reabsorption of Ca^{2+} from the primary urine) and conversely **prevents reabsorption of phosphates** from urine. It also **supports the excretion of HCO_3^-**. As a result, PTH **increases calcemia**, **reduces phosphatemia** and leads to **mild acidosis**.

Parathormone also supports the **formation of calcitriol** – stimulates 1-hydroxylation in the kidneys.

Calcitonin

Calcitonin is a peptide hormone produced by the **parafollicular cells of the thyroid gland** (so-called **C-cells**). It **inhibits osteoclast activity** (inhibits transformation of monocytes to osteoclasts), thereby **reducing bone resorption** and results in **increased deposition of Ca^{2+} in bones**. Concurrently, calcitonin **decreases resorption of Ca^{2+}** and **phosphates in the kidneys**. Both effects lead to a **decrease in calcemia**.

	Calcitriol	Parathormone	Calcitonin
Bones	Ensures availability of Ca^{2+} and phosphate for bones	Osteoclast activation, stimulation of bone resorption and increase in calcemia and phosphatemia	Inhibition of osteoclasts, reduce bone resorption, deposition of Ca^{2+} into bones
Kidney	Slightly reduces the excretion of Ca^{2+}	It reduces the Ca^{2+} excretion (increased resorption), increases excretion of phosphate (prevents resorption), stimulates the production of calcitriol	Decreasing bone resorption of Ca^{2+} and phosphates
Intestine	Stimulates Ca^{2+} resorption	Only indirectly through effect on the formation of calcitriol	–

For more information about parathyroid hormone and calcitonin, see Chapter 11.

Shifts in calcemia – hypocalcemia a hypercalcemia

Hypocalcemia

Hypocalcemia can have these causes:

1) Hypovitaminosis D or hypoparathyroidism

2) Chronic kidney failure

Damaged kidneys fail to form calcitriol (1-hydroxylation) – reduced intestinal absorption of Ca^{2+}. Due to inadequate excretion of phosphates, there in a phosphate accumulation in the body that causes even higher disbalance in Ca/P ratio.

3) Malabsorption

The decrease in extracellular Ca^{2+} concentration can lead to **cramps** (Ca^{2+} stabilizes cell membranes, thus increasing neuromuscular irritability).

Hypercalcemia

The causes of hypercalcemia include hyperparathyroidism or bone diseases (e.g. tumors). Its symptoms are polyuria, somnolence, muscle fatigue and constipation. It can lead to cardiac arrest in systole.

Phosphates

The human body generally contains about **700 g of phosphates**. About **80%** is in the **bones** and **teeth**. Phosphates (serum concentrations of **0.7-1.5 mmol/l**) perform many **functions** in the body:

1) Constituent part of osseous tissue and teeth

2) Contained in vital organic compounds – phospholipids, ATP, nucleic acids, phosphorylated carbohydrates.

3) Buffer

Reabsorption and excretion of phosphates

We receive daily through our diet 800-1400 mg of phosphates, from which 60-80 % is absorbed in the intestine.

Phosphates are freely filtered into the primary urine. In the **proximal tubule** is resorbed more than 80 %, this process is regulated by **parathyroid hormone**.

Shifts in phosphatemia – hyperphosphatemia and hypophosphatemia

Hyperphosphatemia can have the following causes – kidney failure, hypoparathyroidism, vitamin D intoxication. Hypophosphatemia has these causes – hyperparathyroidism, hypovitaminosis D.

Subchapter Authors: Petra Lavríková and Josef Fontana

The clinical use of albumin: the point of view of a specialist in intensive care

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Introduction

In the last decades, research on albumin and its administration to critically ill patients have increased considerably, both in clinical and experimental settings. The observations obtained in research ground have gradually led, on the one hand, to important results[1] with a potential clinical impact on the treatment of different pathological conditions, and, on the other hand, to discussions and controversies[2-4]. It is, therefore, mandatory to ask ourselves whether it is really so important to "care" about albumin when dealing with clinical research in intensive care and, if so, why. A rapid glance at the bulk of data available on the topic may guide the answer to these questions. In fact, it is very interesting to discover that a search for publications on "albumin" in Medline, as updated on October 2008, yields 158,083 items, which is surprisingly greater than the number of publications on "haemoglobin" (120,250), a protein that is undoubtedly quite important in human physiology and pathophysiology! Moreover, it is worth noting that almost 40% of all the publications on albumin have been concentrated in the last 10 years, once again underlying, as mentioned above, how "hot" and current this topic may be considered.

The beginning of the research on the applicability of albumin in clinical practice has generally been ascribed to World War II, with the first case series of seven very severely burned patients treated with intravenous administration of human albumin after they had been injured during the Pearl Harbour attack[5]. Actually, the first report of clinical use of human albumin in a patient with traumatic shock had been made few months before, as results from the archives of the Office of Medical History of the United States (http://history.amedd.army.mil/). The case reported concerned a 20-years old man admitted to the Walter Reed General Hospital in Washington D.C. "*after he had sustained bilateral compound fractures of tibia and fibula and fractures of five ribs; and associated pleural damage, pneumothorax, and subcutaneous emphysema*". The patient appeared confused and had severe systemic hypotension. After he had received two units of human albumin (for a total amount of about 50 g) over a short period of time (about 30 min), his systemic arterial pressure recovered progressively, and 2 hours later, once his main fractures had also been stabilised, the patient appeared to be completely normotensive. The report described successful complete fluid resuscitation during the next day with a further amount of crystalloids. Of note, at no time after intravenous administration of human albumin was there any evidence of allergic reactions and/or circulatory failure, which had been the main obstacles during a previous research project on bovine-derived albumin.

Thus, this first clinical case presented all the potentially important primary and secondary functions of albumin, such as its critical role in determining intravascular oncotic pressure and, on the other hand, its anti-inflammatory properties. From that first case on, many steps have been taken towards a precise clarification of all the characteristics of human albumin with a potential clinical impact in treating critically ill patients. In the present article, we will briefly review the clinical use of human albumin in intensive care medicine and present our point of view on this subject. To this purpose, we will first summarise the physiology and pathophysiology of

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albumin, we will then given an overview of the evidence currently available on its clinical use, and finally we will discuss the potential clinical indications for its administration, also reporting the design of a new clinical trial recently started in Italy.

Physiology and pathophysiology of albumin in humans

In humans, albumin is a protein with a molecular weight of 66,500 Daltons, and accounts for about 50% of the overall content of plasma protein. As a result of its molecular structure and its concentration, albumin is responsible for about 80% of the intravascular oncotic pressure[6].

Metabolism

The metabolism of albumin appears to reflect its importance in human physiology. In fact, under stimulation of the neuroendocrine system and the actual intravascular oncotic pressure, in adults the liver produces about 10-12 g of albumin each day, which is immediately secreted into the intravascular space by the cells without being stored[7]. The entire process of synthesis and secretion of albumin is quite rapid, taking about 30 minutes[8-10]. After entering the intravascular space, about 7 g/h of albumin passes into the interstitial space to different degrees and at different rates depending on the anatomical location, in a process called "transcapillary filtration"[11,12]. In regions characterised by endothelium with large gaps, the filtration of albumin is passive[13], while in regions with non-fenestrated endothelium, its filtration is active[14], under the particular action of a specific receptor, i.e., albondin[15]. The lack of albondin in some anatomical compartments, such as the brain, accounts for the low concentration of this protein in the cerebrospinal fluid[16]. The passage of albumin between the intravascular and the interstitial spaces is a continuous process, with a return to the blood-stream through the action of lymph drainage. At the end of the entire process, albumin is usually degraded ubiquitously, in an amount comparable to that synthesised by the liver (10-12 g/24 h)[17]. *Per se*, the rate of synthesis and degradation may be regulated at various levels. The actual intravascular oncotic pressure is considered one of the simplest mechanisms of regulation, although a clear understanding of its physiological basis has not yet been reached[18-20]. With regards to critically ill patients, it is worth noting that traumatic events, infections or any clinical conditions activating an inflammatory process may repress albumin synthesis[21-28].

Functions

The molecular structure of albumin has three main characteristics which may be considered important for critically ill patients[17]: (i) cysteine residues, (ii) domains I and II, and (iii) imidazole residues. Cysteine residues in position 34 expose a –SH radical group (thiol), which is one of the main extracellular antioxidants[29]. From this point of view, the administration of albumin to a critically ill patient during an acute pathological process usually increases the plasma concentration of thiols[30]. Moreover, –SH residues bind nitric oxide to form S-nitrous thiols, thereby neutralising one of the most important mediators of pathological conditions such as sepsis[31]. Albumin domains I and II are responsible for the transport of the numerous molecules, both endogenous and exogenous, that are extensively carried by human albumin[32]. In this regard, it is evident how albumin concentration may be important when administering drugs with a high-binding affinity, especially during acute pathological processes usually characterised by hypoalbuminaemia. In these conditions, drug toxicity or even drug inefficiency may be observed[33]. Finally, albumin has 16 histidine imidazole residues, which are responsible for the buffer function of albumin. In fact, having a pH of about 6.75, the residues may both give up or accept H^+ from the environment depending on the surrounding pH, thereby acting as a buffer molecule[34].

Pathophysiology in the critically ill

After the above overview of the physiology of albumin, we may wonder which functions are really important for the critically ill.

There is no doubt that the oncotic properties of this protein play a critical role in regulating volaemic status during clinical conditions in which volaemia is very often altered. Nonetheless, in our opinion, during critical and acute conditions, such as sepsis, infections, acute respiratory failure and others, the secondary functions of albumin, as well as the maintenance of its concentration within normal ranges, are of paramount importance.

A few examples may clarify this concept. Most of the pathological conditions in critically ill patients are

characterised by high oxidative stress. From this point of view, an essential function of albumin is to neutralise toxic compounds such as oxygen radicals and nitrite peroxides, through the action, as mentioned above, of -SH residues. Besides this action, albumin may also neutralise the vasodilating effect of nitric oxide, which may be considered the most important mediator altering vascular tone during sepsis or other pathological conditions such as hepatorenal syndrome[35]. Finally, many clinical disorders commonly encountered in intensive care units (ICU) are characterised by metabolic acidosis, in which cellular energy deficits with the production of lactic acidosis may occur. In these conditions, the presence of albumin may help to minimise wide variations of pH, especially in the extravascular space, in which albumin is the only protein with a buffer action.

The most commonly observed pathological alteration in albumin concentration in the critically ill is hypoalbuminaemia[4,33], which is usually defined as a plasma concentration of albumin below 40 g/L. Indeed, one of the main reasons for the widespread administration of albumin has been the evident strong association between hypoalbuminaemia and mortality in various clinical settings, in both acute and chronically ill patients, as well as in young and older subjects[6,36,37].

A reduction of albumin concentration is usually considered the result of decreased production, increased wasting, or an association of the two. In our opinion, however, this simplistic interpretation is incorrect, as it does not take into account the possible alteration of the "solvent", i.e., volaemia, in which the "solute", i.e., albumin, is dispersed, and does not take into account the possible distribution of albumin within the interstitial space. In fact, considering these two further abnormalities, hypoalbuminaemia may be considered the result of: (i) a decrease in its absolute content; (ii) altered water metabolism; and (iii) a redistribution from the intravascular to the interstitial space, due to increased capillary permeability. Thus, although hypoalbuminaemia is very commonly observed in critically ill patients, the dilemma is whether this alteration may really have an impact on the outcome of such patients. In other words, the real question is whether the relationship between hypoalbuminaemia and mortality is a simple association or a cause-effect relation, and, if the latter is the case, what the best cure for hypoalbuminaemia is.

Overview of the evidence available in the literature

In the attempt to determine whether hypoalbuminaemia, or, more in general, any alteration of plasma albumin concentration may affect the outcome of critically ill patients, we must consider the information available in the literature about this topic. Looking at the bulk of publications and, in particular, meta-analyses recently performed, we can conclude that we are in an era of meta-analyses. In fact, starting from the 1990s, when increased attention to cost/benefit analyses of medical treatments led to an extensive review of the indications for albumin administration, there has been a real outburst of research on this subject.

The era of meta-analyses

Everything started in 1998, when a Cochrane report based on a meta-analysis suggested the potentially harmful effect of albumin administration as compared to other fluids for volume replacement[2]. The meta-analysis, published in the British Medical Journal, included 32 clinical trials involving a total of 1,419 patients, and showed, among patients with surgery- or trauma-induced hypovolaemia, no differences in mortality between those treated with albumin and those treated with crystalloids. In contrast, patients with burns who were treated with albumin appeared to have a higher mortality rate as compared to those treated with crystalloids. When the different categories of patients were grouped together, albumin administration was observed to be associated with an increased overall mortality rate as compared to the rate in patients treated with other forms of fluid replacement. The impact of this meta-analysis on the scientific community was dramatic, and led to an extensive reduction of the use of albumin in some countries[38]. At the same time, as usually occurs with such types of analysis, many criticisms were made about the publication, especially regarding the process of study selection, the heterogeneity of the patients included and the limited number of trials considered with a sufficiently high number of subjects. Applying similar selection criteria, another meta-analysis was published in 2001, concluding that albumin administration was safe, although it had no effects on global mortality[3]. Finally, a further meta-analysis, which included nine prospective, randomised clinical

trials on critically ill patients with hypoalbuminaemia, was concluded and published in 2003[4]. This meta-analysis showed a strong, albeit not statistically significant, trend in favour of albumin administration. A statistically significant correlation was, however, observed between the rate of complications and the plasma level of albumin; similarly, the authors observed a lower rate of complications in patients treated with albumin infusion as compared to the control group in the five studies in which plasma albumin concentration was greater than 30 g/L, in contrast to what was observed in the three studies in which plasma albumin concentration was lower than 30 g/L.

In summary, the meta-analyses on the clinical use of albumin in critically ill patients produced completely opposite and controversial results. In fact, of the three largest studies concluded, the first appeared to be against[2], the second one neutral[3] and the third one in favour of the clinical use of albumin[4]. The conclusions of the three studies mentioned above once again highlight the contrasting nature of the findings obtained, and the relatively weak evidence obtained many times from such a type of analysis. While the authors of the first meta-analysis concluded that "*There is no evidence that the administration of albumin reduces mortality in critically ill patients with hypovolemia, burns, hypoalbuminemia, but rather a strong indication that it increases mortality*"[2], the authors of the second meta-analysis concluded that "*our results show that albumin is safe*"[3], and those of the third concluded: "*Currently there is no reason for not administering albumin when clinically appropriate.*"[4].

The SAFE study

To resolve the contradictory findings obtained from these meta-analyses, 16 ICU in Australia and New Zealand conducted a prospective, randomised, double-blind study, the Saline vs. Albumin Evaluation (SAFE) study, comparing the effects of the infusion of 4% albumin and saline solution (0.9% NaCl) for volume replacement in critically ill patients with hypovolemia[1]. According to the study design, the volume infused and the rate of administration were decided by the physicians taking care of the patients enrolled, in accordance with the clinical status and the response to treatment. The primary end-point was mortality rate 28 days after enrolment. Moreover, 28-day mortality rate was also analyzed in three predefined subgroups of patients with specific diseases, i.e., sepsis, trauma and acute respiratory distress syndrome. After the enrolment of about 7,000 patients, no difference in 28-day mortality, length of stay, or organ dysfunction was observed between the groups of patients receiving the two different treatment, thereby clearly demonstrating that 4% albumin infusion employed for volume replacement in a general population of critically ill patients does not offer any advantage as compared to normal saline, or, in other words, that albumin administration is "safe". Although the SAFE study had the potential to overcome several limitations of the previous meta-analyses (with the enrolment of an adequate number of patients, an accurate randomisation process, and a uniform methodology of dosages and administration), it should be acknowledged that some problems remained, particularly in the study design: the study population was heterogeneous, the degree of the severity of illness was moderate, and the amount of fluid administered for volume replacement was relatively moderate. Nonetheless, the great contribution of this study came from the subgroup analysis performed. In fact, while patients with trauma, especially after head injury, treated with albumin tended to have a higher mortality rate ($P = 0.06$), those with severe sepsis tended to show a better survival, although the difference did not reach statistical significance ($P = 0.09$). Thus, for the first time, the attention of researchers was moved towards the possible crucial role of different categories of patients, when dealing with the type of fluid to be employed for volume replacement.

The Dubois study

In 2006, another important study on the effects of albumin administration in critically ill patients was concluded and published in Critical Care Medicine[39]. This study investigated the hypothesis that correcting hypoalbuminaemia in critically ill patients in an attempt to maintain plasma albumin concentration within the normal range (greater than 30 g/L) may have beneficial effects on organ function. Patients were randomised to receive 300 mL of 20% albumin solution on the first day after randomisation and 200 mL/day if their plasma albumin concentration was lower than 31 g/L in the treated group, or to receive no albumin infusion in the control group. The primary

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end-point was organ function, as measured by the Sequential Organ Failure Assessment (SOFA)[41] score, from day 1 to day 7. After enrolment of 100 hypoalbuminaemic patients, the authors first observed a significant separation in plasma albumin concentration between the two groups of patients, with a constant increase in plasma albumin concentrations in treated patients. Moreover, patients treated with albumin infusion showed a greater improvement in organ function than that observed in the control group, mainly due to differences in the respiratory, cardiovascular and central nervous system components of the SOFA score. The authors, therefore, concluded that "*Albumin administration may improve organ function in hypoalbuminaemic critically ill patients*"[39]. Although it was not free of limitations, such as the relatively small number of patients included (and enrolled from just a single centre), and the heterogeneity of the patients randomised, this study is quite important. In fact, it provided, for the first time, some evidence about the critical role of maintaining plasma albumin concentrations within a normal range, throughout the ICU admission, with a possible impact on organ function.

Clinical indications

After this brief summary of what has been more or less clearly established regarding the possible effects of albumin administration in critically ill patients, we should consider the possible clinical indications for using this product. As clearly stated in the last recommendations on albumin administration recently published by the Italian Society of Transfusion Medicine and Immunohaematology, "*the potential limit of all these studies may reside in having grouped different and heterogeneous categories of patients…*"[40].

In our opinion, this is one of the most important and key statements regarding the possible clinical indications for albumin administration. This may be even more important when applying any possible recommendation on the use of albumin to patients admitted to an ICU, as one of the great peculiarities of this category of patients is precisely their heterogeneity. Based on these considerations, as well as on the evidence now available in critically ill patients, we think that there three important categories of critically ill patients for whom specific clinical recommendations regarding the use or not of albumin may be made: patients with traumatic brain injury, patients with peripheral oedema during their recovery phase, and patients with severe sepsis.

Patients with traumatic brain injury

As mentioned above, the SAFE study suggested that trauma patients, especially those with traumatic brain injury, treated with albumin infusion had a higher 28-day mortality rate than that of patients treated with normal saline[1]. In order to further examine this aspect, the same investigators conducted a post-hoc follow-up of the patients with traumatic brain injury previously enrolled in the SAFE study, determining their vital status and functional neurological outcome until 24 months after the randomisation[42]. In detail, 460 patients were followed-up, of whom about 70% were classified as having severe brain injury (with a Glasgow Coma Scale score between 3 and 8). At 24 months after enrolment, the mortality rate of patients treated with albumin appeared to be higher than that of patients treated with saline (33.2% vs. 20.4%, $p = 0.003$), and similar findings were observed in patients with severe traumatic brain injury, with mortality rates of 41.8% and 22.2% in patients treated with albumin or saline, respectively ($p < 0.001$). The authors, therefore, concluded that "*in this post hoc study of critically ill patients with traumatic brain injury, fluid resuscitation with albumin was associated with higher mortality rates than was resuscitation with saline*"[42]. Although these findings may appear disappointing, we should actually be rather pleased with them, as they very likely enable the first really clear recommendation regarding the use or avoidance of albumin in critically ill patients. In fact, based on the findings summarised above, we may clearly state that in this specific category of critically ill patient, i.e., patients with an active brain injury due to cerebral trauma, albumin administration should be avoided, preferring other types of fluids, such as normal saline, for acute volume resuscitation.

Patients with peripheral oedema during their recovery phase

Albumin has usually been studied in humans as a plasma substitute for volume replacement. From this point of view, the volume effect in itself, when taking into account the different characteristics of the types of fluid considered, is identical for albumin, other

forms of colloids, and crystalloids[17]. Nonetheless, at equal intravascular volumes, potential complications and advantages may depend on the different properties of the infused fluid. For example, when employing mainly crystalloids for volume replacement, the most important disadvantage is probably the greater amount of fluids to be infused in order to reach the same volume effect of albumin or other synthetic colloids, with a consequent increased risk of peripheral oedema and weight gain. On the other hand, artificial colloids may alter coagulation, essentially because of absorption of the factor VII/von Willebrand factor complex, with consequent altered platelet aggregation[43], and may lead to an increased risk of developing acute renal failure, as recently observed[43].

Along the same line of reasoning, the role of albumin, especially because of its oncotic properties, may gain even greater importance in the clinical phase that usually follows the acute phase of volume replacement and resuscitation, i.e., the recovery phase, in which, having obtained clinical stability in terms of haemodynamics and organ function, the clinical priority is normally elimination of the excessive fluid previously accumulated in the interstitial space during the resuscitation phase. The intravascular plasma concentration of albumin may be critical during the recovery phase, as it accounts for about 80% of the entire oncotic pressure of the intravascular space[6], as mentioned above. Moreover, the pathophysiological rationale for intravenous administration of albumin during this phase may be more solid than that for administration during the acute phase, as the increased permeability of the capillary barrier that usually characterises the acute florid phase during volume replacement tends to normalise. The albumin infused in this situation is, therefore, more likely to "remain" within the intravascular space than usually occurs during the acute phase. Unfortunately, no clear evidence from randomised clinical trials or other forms of large studies are currently available, probably because of the difficulty of designing studies to investigate such a heterogeneous issue. Nonetheless, in our opinion, the soundness of the biological and pathophysiological rationale may at least partially justify such an indication for albumin administration.

The following case report may help to elucidate this issue. A patient was admitted to our post-surgery ICU after he had admitted for 7 days in a neurological ICU because of traumatic spinal shock. On admission, the patient appeared to be in an oedematous state, with peripheral oedema and bilateral pleural effusion (despite a water restriction programme applied a few days previously), hypotension, oligo-anuria, and systemic arterial hypoxia. The patient's plasma albumin concentration was 13 g/L. We interpreted the patient's clinical situation as a state of anasarca in great need of elimination of the excessive accumulated fluid, probably as a consequence of the volume necessarily administered during the acute phase of the haemodynamic shock. We, therefore, continued the strategy of water restriction, but we initiated albumin administration at the maximal dose usually employed in our institution, i.e., 60 g/day, in association with a low dose of dopamine, in an attempt to obtain a higher mean arterial pressure. Within the following few days, we were able to increase the plasma albumin concentration to about 25 g/L, and we observed a parallel increase in mean arterial pressure and a marked increase of diuresis, with the possibility of obtaining a negative daily fluid balance. In association with these improvements, respiratory function ameliorated, with a significant increase of the ratio of arterial oxygen partial pressure to inspiratory oxygen fraction (PaO_2/FiO_2).

Although clear evidence derived from randomised clinical trials is still lacking with this regard, we may conclude in favour of a possible clinical benefit of albumin administration in patients with marked hypoalbuminaemia, peripheral oedema, and in serious need of water elimination, especially in their recovery phase after acute volume replacement. Although this statement may appear in open contrast with what is called "evidence-based medicine", we consider it important to highlight how lack of evidence may not necessarily exclude the possible beneficial effect of an intervention, especially when a solid pathophysiological rationale is clearly present.

Patients with severe sepsis –the ALBIOS study

Sepsis is a very dramatic syndrome commonly affecting most patients admitted to ICUs. This pathophysiological process involves many inflammatory mediators which have been considered responsible for the haemodynamic alterations and energy failure, as well the multi-organ dysfunction commonly characterising this syndrome. From this point of view, it is now well accepted that, besides its oncotic properties, albumin may play a critical role

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in aiding the normalisation of many of the inflammatory pathways potentially involved in the development of sepsis through its secondary functions, such as the modulating action on nitric oxide metabolism and free radical production[30,31], its buffer effect in the acid-base equilibrium[34], and its action as a transporter of many different substances and drugs[32]. These secondary functions may partially account for the positive trend towards a lower mortality rate observed in the subgroup of patients with severe sepsis treated with albumin, as compared to the control group, during the SAFE study[1]. Unfortunately, essentially due to a small sample size, the difference in mortality rate was not statistically significant, thereby not allowing any conclusions to be drawn on the matter. Similarly, the study by Dubois and colleagues[39], although clearly suggesting that maintaining plasma albumin concentration within the normal range could reduce organ dysfunction, also included a small number of patients and was performed in a single centre, making it impossible to extend the findings to a common general population of critically ill patients.

Based on these considerations, we have recently designed and begun a randomised, multicentre controlled study on the efficacy of albumin administration for volume replacement in patients with severe sepsis or septic shock (ALBumin Italian Outcome Sepsis –ALBIOS –study, EudraCT number 2008-003281-25, ClinicalTrials.gov number NCT00707122). This study, involving about 150 Italian ICU, aims to verify whether volume replacement with albumin and maintenance of plasma albumin concentrations within the physiological range may have beneficial effects in terms of mortality, morbidity and length of stay in patients with severe sepsis or septic shock, as compared to standard volume replacement with crystalloids. To overcome the possible bias derived from potential differences in volume effect of the two strategies, the study design includes two important features: (i) in both arms of the study population, i.e., patients treated with either albumin or crystalloids, volume replacement is performed according to the recent guidelines on the clinical treatment of septic patients[45], in other words according to the "early-goal directed therapy"[46]; (ii) during volume replacement and for the following days of treatment until the 28th day of admission in the ICU (or until the day of discharge from the ICU, whichever comes first), serum albumin level is monitored and kept to a level of 30 g/L or above only in the albumin-treated group[39]. In particular, patients in the albumin group will receive, after randomisation and simultaneously to volume replacement, 300 mL of 20% albumin solution (total amount, 60 g). From day 2 to day 28 (or until discharge from the ICU, whichever comes first), if the patients' serum albumin concentration is equal to or higher than 25 g/L and below 30 g/L, they will receive 200 mL of 20% albumin solution (total amount, 40 g); if the serum albumin concentration is below 25 g/L, they will receive 300 mL of 20% albumin solution (total amount, 60 g). Moreover, further infusions of crystalloids will be allowed, when necessary, according to clinical judgment. In contrast, patients included in the control group will receive only crystalloids both during the volume replacement phase as well as from day 2 to day 28 (or until ICU discharge, whichever comes first). No infusion of colloids, other than albumin, will be allowed in either group. The primary objective of the study is to verify the hypothesis that volume replacement with albumin and maintenance of plasma albumin levels within the predefined physiological range improves survival of patients with severe sepsis or septic shock, as compared to a volume replacement with the use of crystalloids, measured until the 28th and 90th day after randomisation. Secondary objectives are to determine whether this strategy reduces the number and severity of organ dysfunctions (as assessed by the SOFA score[41]), the time spent in the ICU, and the duration of hospital stay.

We think it is important to highlight the potential advantages of the study design. First of all, the introduction of the "early-goal directed therapy"[45] both in patients treated with albumin and in those given crystalloids, with the use of pre-defined haemodynamic targets, will standardise and optimise volume replacement for all the septic patients according to the standard of care currently suggested worldwide. Second, it will allow us to specifically observe the direct effects of albumin administration *per se* and the maintenance of its serum level within the normal range. In other words, this study design will allow us to specifically elucidate the possible role of the secondary functions of albumin on the pathophysiology of severe sepsis and, therefore, their potential impact on outcome. The study has just

started, with the randomisation of the first patient at the end of August 2008, and is planned to be completed in about 2-3 years, with an expected enrolment of about 1350 patients (for more details, see www.clinicaltrials.gov).

Conclusions

In the past decades, the research on albumin for the clinical treatment of critically ill patients has certainly yielded important information aiding more appropriate use of this product. It is now evident and quite well accepted that, apart from its oncotic properties, albumin has secondary functions that may play a critical role and have a great impact on different types of diseases. At the moment, based on the evidence currently available, we can state that albumin is not necessary for normal volume replacement in moderate critically ill patients and, furthermore, that it should be avoided in patients with traumatic brain injury[42]. In contrast, in patients with severe hypoalbuminaemia and peripheral oedema during the recovery phase after acute volume replacement, albumin administration may have a beneficial impact, especially on the elimination of the excessive accumulated volume. Finally, one of the most important categories of patients for which preliminary results suggest a potential beneficial role of albumin on outcome is that of patients with severe sepsis[1]. Whether of not this is the case should be demonstrated in the near future by a recently started, large, randomised clinical trial.

Key words: albumin, critically ill, sepsis, fluid resuscitation, traumatic brain injury

References

1) Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;**350**:2247-56.
2) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. BMJ 1998;**317**:235-40.
3) Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 2001;**135**:149-64.
4) Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 2003;**237**:319-34.
5) Peters T. Historical perspective. All about albumin. San Diego, California: Academic Press Limited; 1996:1-8.
6) Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. Crit Care Med 1979;**7**:113-6.
7) Schomerus H, Mayer G. Synthesis rates of albumin and fibrinogen in patients with protein-losing enteropathy and in a patient recovering from protein malnutrition. Digestion 1975;**13**:201-8.
8) Hafkenscheid JC, Yap SH, van Tongeren JH. Measurement of the rate of synthesis of albumin with 14C-carbonate: a simplified method. Z Klin Chem Klin Biochem 1973;**11**:147-51.
9) Gersovitz M, Munro HN, Udall J, Young VR. Albumin synthesis in young and elderly subjects using a new stable isotope methodology: response to level of protein intake. Metabolism 1980;**29**:1075-86.
10) Ballmer PE, McNurlan MA, Milne E, et al. Measurement of albumin synthesis in humans: a new approach employing stable isotopes. Am J Physiol 1990;**259**:E797-803.
11) Peters T. Metabolism: albumin in the body. All about albumin. San Diego, California: Academic Press Limited; 1996:188-250.
12) Beeken WL, Volwiler W, Goldsworthy PD, et al. Studies of I-131-albumin catabolism and distribution in normal young male adults. J Clin Invest 1962;**41**:1312-33.
13) Ganong W. Dynamics of blood and lymph flow. Review of medical physiology. Collecticut: Appleton and Lange; 1995:525-41.
14) Peters T Jr. Biosynthesis of rat serum albumin. VII. Effects observed in liver slices. Am J Physiol 1973;**224**:1363-8.
15) Schnitzer JE, Oh P. Albondin-mediated capillary permeability to albumin. Differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. J Biol Chem 1994;**269**:6072-82.
16) Pardridge WM, Eisenberg J, Cefalu WT. Absence of albumin receptor on brain capillaries in vivo or in vitro. Am J Physiol 1985;**249**:E264-7.
17) Gattinoni L, Carlesso E, Caironi P. [Albumin administration: volume replacement or pharmacological treatment?]. Minerva Anestesiol 2005;**71**:27-40.
18) Rothschild MA, Oratz M, Mongelli J, Schreiber SS. Effect of albumin concentration on albumin synthesis in the perfused liver. Am J Physiol 1969;**216**:1127-30.
19) Dich J, Hansen SE, Thieden HI. Effect of albumin concentration and colloid osmotic pressure on albumin synthesis in the perfused rat liver. Acta Physiol Scand 1973;**89**:352-8.
20) Schmid M, Schindler R, Weigand K. Is albumin synthesis regulated by the colloid osmotic pressure? Effect of albumin and dextran on albumin and total protein synthesis in isolated rat hepatocytes. Klin Wochenschr 1986;**64**:23-8.
21) Pietrangelo A, Panduro A, Chowdhury JR, Shafritz DA. Albumin gene expression is down-regulated by albumin or macromolecule infusion in the rat. J Clin Invest 1992;**89**:1755-60.
22) Cairo G, Schiaffonati L, Aletti MG, Bernelli-Zazzera A. Effect of post-ischaemic recovery on albumin

synthesis and relative amount of translatable albumin messenger RNA in rat liver. Biochem J 1982; **204**:197-202.

23) Liao WS, Jefferson LS, Taylor JM. Changes in plasma albumin concentration, synthesis rate, and mRNA level during acute inflammation. Am J Physiol 1986;**251**:C928-34.

24) Milland J, Tsykin A, Thomas T, et al. Gene expression in regenerating and acute-phase rat liver. Am J Physiol 1990;**259**:G340-7.

25) Ozaki I, Motomura M, Setoguchi Y, et al. Albumin mRNA expression in human liver diseases and its correlation to serum albumin concentration. Gastroenterol Jpn 1991;**26**:472-6.

26) Ramadori G, Van Damme J, Rieder H, Meyer zum Buschenfelde KH. Interleukin 6, the third mediator of acute-phase reaction, modulates hepatic protein synthesis in human and mouse. Comparison with interleukin 1 beta and tumor necrosis factor-alpha. Eur J Immunol 1988;**18**:1259-64.

27) Castell JV, Gomez-Lechon MJ, David M, et al. Acute-phase response of human hepatocytes: regulation of acute-phase protein synthesis by interleukin-6. Hepatology 1990;**12**:1179-86.

28) Brenner DA, Buck M, Feitelberg SP, Chojkier M. Tumor necrosis factor-alpha inhibits albumin gene expression in a murine model of cachexia. J Clin Invest 1990;**85**:248-55.

29) King TP. On the sulfhydryl group of human plasma albumin. J Biol Chem 1961;**236**:C5.

30) Quinlan GJ, Margarson MP, Mumby S, et al. Administration of albumin to patients with sepsis syndrome: a possible beneficial role in plasma thiol repletion. Clin Sci (Lond) 1998;**95**:459-65.

31) Stamler JS, Jaraki O, Osborne J, et al. Nitric oxide circulates in mammalian plasma primarily as an S-nitroso adduct of serum albumin. Proc. Natl Acad Sci USA 1992;**89**:7674-7.

32) Sudlow G, Birkett DJ, Wade DN. The characterization of two specific drug binding sites on human serum albumin. Mol Pharmacol 1975;**11**:824-32.

33) Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000; **85**:599-610.

34) Reeves RB. Temperature-induced changes in blood acid-base status: Donnan rCl and red cell volume. J Appl Physiol 1976;**40**:762-7.

35) Hori N, Wiest R, Groszmann RJ. Enhanced release of nitric oxide in response to changes in flow and shear stress in the superior mesenteric arteries of portal hypertensive rats. Hepatology 1998;**28**:1467-73.

36) Powers KA, Kapus A, Khadaroo RG, et al. Twenty-five percent albumin prevents lung injury following shock/resuscitation. Crit Care Med 2003;**31**:2355-63.

37) Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997;**50**:693-703.

38) Roberts I, Bunn F. Egg on their faces. The story of human albumin solution. Eval Health Prof 2002; **25**:130-8.

39) Dubois MJ, Orellana-Jimenez C, Melot C, et al. Albumin administration improves organ function in critically ill hypoalbuminemic patients: a prospective, randomized, controlled, pilot study. Crit Care Med 2006;**34**:2536-40.

40) Liumbruno GM, Bennardello F, Lattanzio A. et al. Recommendations for the use of albumin and immunoglobulins. Blood Transfus 2009; **7**: 216-34

41) Vincent JL, de MA, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;**26**:1793-800.

42) Myburgh J, Cooper J, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;**357**:874-84.

43) de Jonge E, Levi M. Effects of different plasma substitutes on blood coagulation: a comparative review. Crit Care Med 2001;**29**:1261-7.

44) Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;**358**:125-39.

45) Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;**36**:296-327.

46) Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;**345**:1368-77.

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Balanced Resuscitation in Trauma Management

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KEYWORDS

• Balanced resuscitation • Trauma • Coagulopathy • Hemorrhagic shock
• Damage control

KEY POINTS

- Crystalloid, once considered central to the resuscitation of traumatic hemorrhagic shock, leads to numerous complications and increases patient morbidity and mortality.
- Trauma-induced coagulopathy is frequent in injured patients at the time of hospital presentation and is worsened by aggressive crystalloid use.
- Balanced resuscitation minimizes coagulopathy through permissive hypotension, restrictive crystalloid use, and high ratios of plasma and platelet to red blood cell transfusion.
- Balanced resuscitation with plasma, platelets, and red blood cells in a 1:1:1 ratio improves outcomes and should be initiated early, including prehospital, when possible.
- Balanced resuscitation can be achieved through the use of preplanned, matured massive transfusion protocols, specifically designed to be continued until actively turned off.

INTRODUCTION

As the leading global cause of death among youth and young adults, the impact of trauma on years of productive life lost cannot be overstated.[1] With only brain injury as a larger cause of overall mortality, hemorrhage is the leading cause of preventable trauma death.[2–6] Rates of mortality in injured patients requiring a massive blood transfusion in the late 1980s were greater than 80%. Prehospital strategies considered standard of care at the time included early intravenous (IV) access with 2 large-bore cannulas and aggressive administration of crystalloid, regardless of patient physiology. In the civilian setting, in which blunt trauma predominates, paramedical, emergency, and surgical trauma providers loyally performed these same resuscitation strategies for several decades. Until recently, they continued to be taught on a global scale. The Advanced Trauma Life Support Course, used as a benchmark international trauma reference and teaching tool, and last updated in 2012, still promotes these

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resuscitation strategies.[7,8] As a result, over the last 30 years, the initial resuscitation of patients with trauma had changed very little. At the start of the new millennium, despite many significant advances, those patients with significant hemorrhage continued to have a mortality of more than 50%.[9]

However, the last decade has witnessed the birth of a new paradigm in early trauma resuscitation. This radical shift emphasizes balanced resuscitation, using ratios of plasma, platelets, and red blood cells (RBCs) that approximate whole blood as early as possible in a patient's care. It has become understood that aggressive crystalloid resuscitation worsens coagulopathy through dilution, contributes to acidosis through pH alteration, and exacerbates hypothermia via infusion of large volumes of cold solution. To address this, a central tenet of balanced resuscitation is to limit early crystalloid use in an attempt to attenuate the predictable metabolic derangements that are associated with this traditional approach. With the addition of permissive hypotension, the third pillar of balanced resuscitation, current mortalities in hemorrhaging patients have decreased to as low as 20% (**Fig. 1**).[10] This article focuses on the balanced resuscitation portion of trauma management. The aim is to understand the motives behind the long-standing use of crystalloid resuscitation, review the advantages and disadvantages of various resuscitative agents, and present the compelling evidence that exists for balanced resuscitation in the management of trauma.

THE HISTORY OF WHOLE-BLOOD AND COMPONENT THERAPY

At the outset of World War 1 (WW1), the British military thought that blood transfusions caused harm and were instead focused on using crystalloids for resuscitation.[11] Concurrently, significant advancements in the tools and techniques necessary for blood typing, anticoagulation, and storage were being made. As a result, by the end of WW1, many casualties were being resuscitated with whole blood and this quickly became the standard of care in several military hospitals. Knowledge of whole blood–based resuscitation continued to evolve during both World War II (WWII) and the Korean War. The British had a functional blood transfusion system in place at the outset of WWII and the United States military shortly followed suit. By the end of WWII, the American military was mobilizing massive volumes of blood for transfusion. The American Red Cross drew more than 13 million units of whole blood from

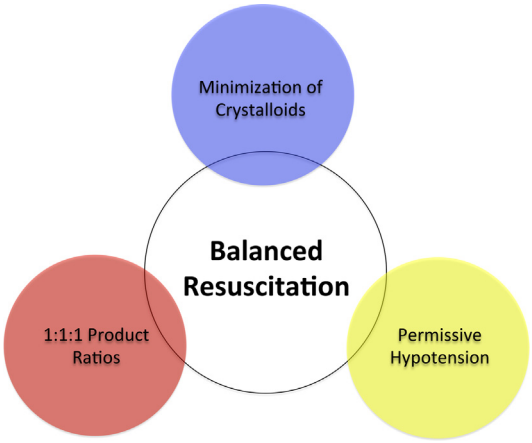

Fig. 1. The 3 tenets of balanced resuscitation.

donors during this war.[11] However, product waste was common. For example, during both the Korean War and the Vietnam War product waste was estimated at greater than 50%. Although fractionated products, including fresh frozen plasma (FFP), became available during the Vietnam War, going forward the United States military focused primarily on the procurement, transport, and storage of large volumes of RBCs. Despite this, fresh whole blood remained a useful tool because it could be readily procured from front-line soldiers and avoided the limitation of physical storage needed for component products. Furthermore, colloids, such as hydroxyethyl starch, with their significant ability to increase circulating volume and their reduced weight compared with crystalloids, were being developed and were touted as advantageous for the transport needs required in the conflict environment.[12]

In the civilian setting, in which concerns about the volume and weight of fluids used for resuscitation are minimal, storage of large quantities of product in centralized blood banks and dedicated care centers is efficient and practical. Whole blood, depending on the anticoagulant used, can be refrigerated and stored on average for 4 weeks. Using component separation, RBCs can be stored at 2°C to 6°C for 6 weeks while still maintaining viability, and FFP (plasma that has been frozen within 8 hours of collection) can be stored at −18°C for 1 year or at −65°C for 7 years.[13,14] Plasma separation from whole blood therefore significantly extends its useful lifespan. Once thawed, plasma can be kept refrigerated at 1°C to 6°C for a further 5 days while still retaining useful levels of coagulation factors.[15] In the United States, platelets are stored at room temperature for 5 days, at which point they must be discarded secondary to possible bacterial contamination.[16] Fractionation also provides the advantage of targeting components for specific clinical use, including those outside of trauma and resuscitation, for which individual components rather than whole blood may be desired (**Fig. 2**).

Although early work studying transfusion in trauma suggested that component therapy was not necessary to supplement whole blood, once the fractionation of products occurred, RBCs (and large volumes of crystalloid) alone became the standard to resuscitate bleeding patients.[11,17] The contribution of plasma and platelets to trauma

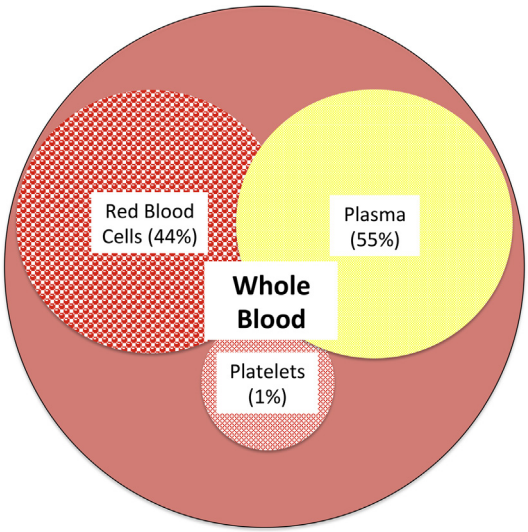

Fig. 2. The 3 primary components of whole blood.

resuscitation was discounted and a strategy of crystalloid first then RBCs later took hold.

THE CRYSTALLOID ADVANTAGE?

Because patients with trauma arrived in the emergency department (ED) without a type and screen and away from the centralized blood bank, early crystalloid therapy provided a means to rapidly resuscitate these patients while blood was being prepared.[18] With this in mind, crystalloid use in trauma resuscitation had several theoretic advantages. Most notably, it was seen as an inexpensive resource that was readily accessible and easily stored. It could be kept in the resuscitation bay or the operating room in quantities limited only by the physical storage space available. It did not require a refrigerator and small volumes could be kept in a warmer and readily replaced. Furthermore, it had an extremely long shelf life, could be mass produced by industry, rarely required being discarded secondary to expiration, and was cheap to restock.

Crystalloids were also familiar agents, used on a daily basis by most nurses and physicians. They required little adaptation for implementation in the resuscitation bay and did not require monitoring for transfusion reactions. Furthermore, crystalloids did not require testing for pathogens, such as human immunodeficiency virus (HIV) and hepatitis, did not pose a risk of blood-borne exposure to either health care workers or patients, and did not need to be typed or cross-matched. An ongoing crystalloid infusion, for the most part, did not require special IV lines or filters. Crystalloids could also be easily implemented in the prehospital setting, in which the advantages were similar, including ease of use, storage, and longevity. Patients could arrive at a resuscitation bay and have the same fluid bag continued while the primary survey was initiated and while improved IV or central venous access was obtained.

In contrast, blood products cannot be mass produced, require complex collection, sensitive screening for blood-borne pathogens, and careful means of transport and storage. They require processing and separation into components and close monitoring for transfusion reactions, both early and delayed. To infuse a blood product, there is a potential delay in order to check the blood band. Their high cost and short shelf life also mean that their use in the prehospital setting is limited, expensive, and potentially wasteful. In many countries, there is a history of significant fear of blood transfusion because of the previous use of tainted products and the infection of many recipients with hepatitis C and, later, HIV in the 1970s and early 1980s.[19,20] This stigma likely further contributed to health care workers' trepidation with transfusions and probably increased their favor for crystalloids. Blood product use decreased in trauma care from 54% of patients receiving product in 1991 to 42% in 1995.[21] The overall number of units being transfused between these 2 time points also decreased significantly.

CRYSTALLOID RESUSCITATION

What was the evidence behind using crystalloid in trauma resuscitation? Clinical experience with the use of crystalloid in elective and emergency surgical patients expanded rapidly in the 1980s and 1990s, and many physicians thought that this resuscitation knowledge was applicable to patients with trauma in hemorrhagic shock. However, the use of these fluids leads to a decrease in osmotic pressure and an increase in capillary permeability. A significant portion of the infused volume is lost from the intravascular space into the interstitium. When considering fluid resuscitation in major surgical operations, Shires and colleagues[22] showed that, with tissue injury, extracellular

volume was lost, independent of blood loss. The degree of extracellular volume loss and internal redistribution seemed to be related to the extent of tissue injury. It was realized that, despite providing intravascular volume, fluid inherently moved out of the intravascular and intracellular spaces and into the extracellular space during tissue trauma, in the form of surgery, and that postoperative extracellular volume was directly related to the amount of intraoperative fluid administered.[23] The focus, therefore, became to maintain or even expand the extracellular volume throughout a major operation, even beyond the fluid volumes that were thought to be necessary for maintenance.[24] This observation of the contraction of extracellular fluid in surgical patients suggested that replacement with balanced salt solutions might be of benefit in trauma resuscitation as well.

Moore and Shires,[25] in a 1967 editorial entitled "Moderation," attempted to stop these aggressive resuscitation strategies before they became standard practice. The investigators raised concern about the use of crystalloid solutions to maximize the intravascular volume and to maintain excess volume in the interstitium so that patients had the necessary volume to replace any potential losses from bleeding. This approach was being used to such an extreme that patients were often receiving more than an entire blood volume equivalent of crystalloid during any major abdominal surgery. Moore and Shires[25] recommended that "replacement during operation should be carefully estimated and limited" and that blood "should still be replaced during major operative surgery as it is lost." The use of balanced salt solutions, they added, "appears to be a physiological adjunct to surgical trauma, not a substitute for blood." What is often lost, and is critical to remember, is that these cautions were coming during a time when the blood being used for trauma and major surgery was whole blood, not simply fractioned components such as RBCs.

Despite this caution, the use of crystalloids for replacement of lost blood gained momentum. Focus became placed on the prophylactic optimization of defined physiologic parameters through intensive, and often invasive, monitoring.[26] These invasive catheters and monitors provided new numbers (cardiac index, pulmonary artery pressures, central venous pressures, and mixed venous oxygen tension) and new laboratory values (lactate level, base deficit) to measure. It was no longer considered enough to simply maintain normal heart rate, blood pressure, and urine output.[27] Establishing and prophylactically maintaining normal patient parameters for each of these criteria in the critically ill population became the norm, even if extremely aggressive resuscitation was required to achieve these supraphysiologic results. At this same time, the idea of the damage-control laparotomy was emerging. This abbreviated laparotomy was initially described to help manage patients with severe physiologic disturbances by leaving them open to return for closure once stable.[28,29] However, surgeons increasingly found that they struggled to close fascia at subsequent explorations and the resultant sequelae of abdominal compartment syndrome began to be seen and treated as a new and accepted entity.[30,31]

The complications of aggressive crystalloid resuscitation were also being recognized to extend well beyond that of abdominal compartment syndrome. Both normal saline and lactated Ringer in large volumes have been shown to contribute to various forms of acidosis. Normal saline leads to a hyperchloremic metabolic acidosis that in turn leads to decreased cardiac contractility, decreased renal perfusion, and less inotropic response, whereas large volumes of lactated Ringer contribute to a compensatory respiratory acidosis.[32–34] An overloaded fluid status has been shown to increase mortality from postoperative pulmonary edema.[35] Studies assessing fluid management strategies in acute lung injury and acute respiratory distress syndrome have found that a conservative use of fluid leads to more ventilator-free days, shorter

intensive care unit (ICU) stays, and improved lung function without increasing failure rates of other organ systems.[36] Although, at small doses, fluid may improve cardiac performance in some populations, aggressive saline resuscitation can further compromise cardiac performance, driving many critically ill surgical patients and patients with trauma off their optimal Starling curve.[37,38] Postoperative patients receiving greater than 3 L of crystalloid at normal saline concentrations have been shown to have delayed gastric emptying time, delayed return of bowel function, prolonged hospital stay, and more perioperative complications compared with a restrictive fluid strategy.[39] Overall, it seems that the downsides of crystalloids are extensive, and, despite their convenience in the trauma bay, they likely do more harm than good in resuscitation for hemorrhagic shock.

COLLOIDS

The advantage of colloids for resuscitation was thought to be that they could significantly and rapidly expand circulating volume. Synthetic options including dextran, starch-based solutions such as hydroxyethyl starch, and plasma-derived albumin all contain large molecules that exert a significant osmotic effect on the surrounding tissue. They effectively draw fluid into the intravascular space from the interstitial and intracellular spaces, resulting in both a maintenance and expansion of the circulating volume in patients with trauma.[40,41] Commonly referred to as plasma expanders, as larger molecule liquids they stay in the intravascular space for a longer period of time and are able to expand intravascular volume more effectively than crystalloids. However, in addition to higher cost of colloids, there are several other downsides compared with crystalloids. There is an uncommon, but recognized, risk of hypersensitivity reaction to these solutions. Dextran is known to reduce platelet aggregation in some populations and has been used as an anticoagulant in the past.[42] Albumin, a byproduct of human blood fractionation, is expensive to produce. The starch-based colloid solutions have been associated with anaphylactoid reactions and with renal failure.[43] Importantly, hydroxyethyl starches have been shown to cause coagulopathy.[44] They reduce maximal clot firmness and reduce all coagulation factor activities, with the greatest impact on fibrinogen and factor II, XIII, and X activity. They are so effective at this that they are used to create dilutional coagulopathy in studies evaluating the efficacy of hemostatic adjuncts.[45]

PLASMA AS THE OPTIMAL RESUSCITATION FLUID

Plasma has long been recognized as an excellent buffer solution.[46] It has been shown to be a 50-fold better buffer than crystalloids and 5-fold better than albumin. This ability, secondary to its high citrate content, makes it ideal for the resuscitation of patients in a state of severe acidosis from shock. In addition to containing all necessary clotting factors and countless microparticles, plasma contains up to 500 mg of fibrinogen per unit.[47] Like colloids, plasma provides the additional benefit of being an excellent volume expander by leading to a significant increase in osmotic pressure. As a result, it increases intravascular volume both directly and indirectly by drawing interstitial and intracellular volume into circulation. Furthermore, plasma has been shown in animal models to have a positive impact on endothelial vascular integrity by stabilizing the endothelial glycocalyx and inhibiting permeability by as much as 10-fold.[48]

So why has its use not been universally adopted? In addition to availability, transfusion-related events, including ABO incompatibility, transfusion reactions, and transmission of infections, have been reported. Plasma also has a high cost of procurement, testing, and storage. Opponents of aggressive plasma resuscitation cite

data that suggest that it leads to a higher incidence of transfusion-related acute lung injury.[49] However, newer, compelling evidence argues that the development of moderate to severe hypoxemia after trauma is more likely to be caused by a patients age, extent of lung injury, and the use of crystalloid resuscitation and shows no relationship with product use, whether it be RBCs, plasma, or platelets transfused.[50] Animal model evidence exists that plasma may mitigate the lung injury sustained from shock compared with crystalloid.[51] Acute lung injury after trauma is much more likely to be caused by hemorrhagic shock and crystalloid resuscitation than by plasma transfusion. Plasma transfusion is likely to be beneficial in this scenario.

THE BALANCED RESUSCITATION STRATEGY

In the setting of hemorrhage, balanced (or damage control) resuscitation refers to the strategy adopted by the US military to improve outcomes of patients undergoing an abbreviated laparotomy or other procedure because of grossly disturbed physiology. As an adjunct to the care of these critically injured patients, its early implementation focused on delivering higher ratios of plasma and platelets, along with other strategies to prevent "popping the clot." Its 3 basic tenets are permissive hypotension, minimizing the use of crystalloid before surgical control of bleeding, and transfusion of blood products in a ratio approximating whole blood.[52] Ideally, this process begins in the prehospital setting, continues through early trauma bay/emergency room resuscitation, and is completed in the operating room or the ICU, as needed.

As massive transfusion protocols (MTPs) developed, studies began to explore outcomes from different product ratios given to patients who ended up requiring more than 10 units of RBCs within a 24-hour period. Work on determining both the ideal plasma to RBC and platelet to RBC ratios was pursued. Examining different MTPs used by different trauma centers and organizations, Malone and colleagues[53] suggested that preemptive treatment of coagulopathy with a 1:1:1 product ratio seems to be associated with improved outcomes and provides the additional benefit of ease of use. Ho and colleagues[54] made a similar argument for this strategy with the aim of transfusing patients with trauma with factors equivalent to whole blood in a timely fashion. In 2008, Holcomb and colleagues[55] published data from 16 civilian trauma centers showing that plasma/RBC and platelet/RBC ratios of greater than 1:2 improved early and late survival, primarily through a reduction in rates of truncal hemorrhage. They concluded that MTPs should target an ideal ratio of 1:1:1. Gunter and colleagues[56] showed that both higher plasma to RBC and higher platelet to RBC ratios each individually improved the 30-day mortality of patients with MT trauma. These data formed the basis for the landmark (The Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial) PROPPR trial. Investigators directly compared the mortality of patients with trauma (predicted to receive MT) randomized to a ratio of 1:1:1 versus 1:1:2.[10] Although the 2 groups did not have a significant difference in 24-hour or 30-day mortality, the 1:1:1 group had fewer deaths caused by bleeding and improved rates of achieving hemostasis. These findings led to the recent Eastern Association for the Surgery of Trauma's (EAST) recommendation for transfusion of equal amounts of RBC, plasma, and platelets during the early, empiric phase of resuscitation.[57]

The role of fibrinogen (concentrate or cryoprecipitate) in the resuscitation of patients with hemorrhagic shock remains unclear. Cryoprecipitate acts as a concentrated source of fibrinogen and other coagulation proteins; however, its transfusion is often delayed for several hours in patients with trauma. Transfusion of cryoprecipitate within 90 minutes of patient arrival has undergone preliminary study that suggests that it is feasible to administer and possibly affects mortality.[58] As a result, a United

Kingdom–funded, multicenter, randomized trial comparing early cryoprecipitate transfusion with standard blood transfusion therapy in severely bleeding patients with trauma is currently underway (CRYOSTAT-2).

PREHOSPITAL RESUSCITATION

In 2011, Haut and colleagues[59] showed, in a review of the National Trauma Data Bank, that patients with trauma who received prehospital IV lines had significantly higher mortality than those who did not. Given the resuscitation and transfusion trends of the time period during which these patient data were collected (2001–2005), it is highly likely that the patients receiving prehospital IV fluid were receiving crystalloid only resuscitation. They were almost certainly not receiving blood products. In the development of guidelines for prehospital fluid administration, EAST found insufficient data to support the administration of prehospital fluids to severely injured patients as well as insufficient data to recommend one type of resuscitation fluid rather than another.[60] In 2015, a randomized study from the Resuscitation Outcomes Consortium compared a standard resuscitation protocol of 2 L of fluid plus additional boluses as needed to maintain a systolic blood pressure of 110 mm Hg or greater against a controlled resuscitation protocol using 250-mL boluses to maintain a radial pulse or a systolic blood pressure of 70 mm Hg or greater.[61] Simultaneously examining 2 of the tenets of hemostatic resuscitation (permissive hypotension and limited crystalloid use), the investigators found that the controlled resuscitation strategy offered an early survival advantage. In the military setting, this concept had previously been proposed by both Cannon and colleagues[62] and Beecher.[63,64] Cannon and colleagues[62] in 1918 reported that the "injection of a fluid that will increase blood pressure has dangers in itself." They argued that, in hemorrhage, if the blood pressure is "raised before the surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost." Beecher,[64] just after WWII, wrote that, before surgical control of bleeding, "elevation of his systolic blood pressure to about 85 mm Hg is all that is, necessary… and when profuse internal bleeding is occurring, it is wasteful of time and blood to attempt to get the patient's blood pressure up to normal."

As emphasis has moved away from prehospital crystalloid use, several recent studies evaluating blood product transfusion (both plasma and RBC) in the prehospital setting have shown that these products are associated with improved early outcomes, with little, if any, wastage.[65] In addition, patients receiving these products arrive with improved acid-base status and a lower incidence of coagulopathy.[65–67] Several centers have since developed and matured their protocols with prehospital products whereby the flight team (nurses and paramedics) may initiate transfusion based on field variables. Both the Mayo Clinic and University of Texas–Houston initiate plasma and RBC transfusion based on the prehospital Assessment of Blood Consumption (ABC) score (**Table 1**).[68,69] Others have recommended the prehospital shock index to guide blood product use.[70]

TRAUMA BAY RESUSCITATION

There is increasing evidence that patients should not be aggressively resuscitated in the prehospital environment and that blood products are of benefit in this setting, so the question becomes how should clinicians resuscitate these patients once they arrive at the trauma center, where definitive hemorrhage control can be attempted and achieved? The data in this setting are more robust, older, and more convincing than the evolving prehospital literature. As early as 1994, the concept of a possible benefit from delayed resuscitation was being considered.

Table 1
Assessment of blood consumption score for the prediction of massive transfusion

Variable	Yes or No? (Yes = 1, No = 0)
1. Penetrating mechanism	Yes/no
2. Positive FAST	Yes/no
3. HR $\geq$ 120 bpm	Yes/no
4. SBP $\leq$ 90 mm Hg	Yes/no
Total out of 4	If $\geq$2 = yes, initiate MTP

Abbreviations: bpm, beats per minute; FAST, focused assessment with sonography for trauma; HR, heart rate; SBP, systolic blood pressure.

Bickell and colleagues[71] reported that patients with penetrating torso injuries who were randomized to delayed fluid resuscitation (no fluid until operating room arrival) had improved survival, shorter hospital stays, and fewer complications than those randomized to immediate crystalloid resuscitation from the scene and during their ED stays. In 2002, Dutton and colleagues[72] reported that the resuscitation of patients presenting with severe hemorrhage to a systolic pressure of greater than 110 mm Hg was not superior to allowing for permissive hypotension with a systolic goal of 70 mm Hg. Mortality was similar between these groups, and permissive hypotension had the potential to allow better control of bleeding with fewer transfusions than the higher target.

As in the prehospital setting, early recognition of the need for MT is important and can be facilitated by scores designed for the prediction of MT, such as the ABC score.[68,73] For balanced resuscitation to be effective, blood products, including plasma and platelets, should be as readily available as RBCs. Ideally, universal thawed plasma is on hand at the time of patient arrival and, to accomplish this, some centers have begun stocking their trauma bays/EDs with plasma, which significantly reduces the time it takes for plasma to be delivered to patients in hemorrhage. Radwan and colleagues[74] showed that having thawed (or liquid) plasma available in the ED was associated with fewer transfusions of RBC, plasma, and platelets in the first 24 hours and was an independent predictor of reduced 30-day mortality in this population. The strategy should therefore be to have thawed AB plasma available in the resuscitation bay to be used until type-specific plasma can be thawed and becomes available from the blood bank. However, to have plasma immediately available is challenging in many centers. If thawed AB plasma in the ED is not feasible or practical, one solution is to use liquid (never frozen) plasma. Liquid plasma has a hemostatic profile that is superior to thawed plasma and it can viably be stored in a refrigerated setting for up to 26 days.[75] The hemostatic ability of this product, and its long refrigerator storage potential, suggest that it may be the ideal product to be kept within the trauma bay where it is close at hand for the resuscitation of hemorrhaging patients with trauma. In addition, although less than 5% of donors are AB blood group, at least 40% of donors are type A and many of them have low enough titers of anti-B that it can be safely given as a universal product. Therefore, liquid AB and low-titer A plasma should be strongly conserved for ED use.

OPERATING ROOM RESUSCITATION

In evaluating all components of damage control resuscitation, including permissive hypotension, limitation of crystalloids, and delivering high ratios of plasma and

platelets, Cotton and colleagues[76] found that those patients with trauma undergoing damage control laparotomy had a significant increase in 30-day survival when this resuscitation strategy was implemented. Morrison and colleagues[77] published randomized data that suggested that the hypotensive resuscitation strategy should potentially extend beyond the trauma bay and into the operating room. They reported that patients with trauma requiring urgent operative intervention required less fluid and blood product when an intraoperative MAP target of 50 mm Hg was used, as opposed to an MAP target of 65 mm Hg, but these patients also had lower rates of early postoperative mortality and a trend toward lower overall mortality. They were also less likely to develop early coagulopathy, less likely to have a severe coagulopathy, and less likely to die from bleeding. The investigators concluded that a hypotensive resuscitation strategy is safe in trauma. Duke and colleagues[78] showed that, as part of a damage control resuscitation strategy, restrictive fluid use in patients with trauma, compared with standard fluid use, led to lower rates of intraoperative mortality and shorter lengths of hospital stay. In addition, the PROPPR trial noted that, compared with patients receiving 1:1:2 ratio, those receiving a 1:1:1 ratio more rapidly achieved clinical hemostasis, had their MTP discontinued sooner, and had lower bleeding-related mortality.[10] Continuing a balanced resuscitation strategy intraoperatively is critical.

One of the intrinsic benefits of an MTP is to provide the resuscitation team with the ability to transfuse patients without having to track product ratios closely during an intense operation and resuscitation. Each MTP pack should be designed to contain a balanced ratio of product and each patient should receive 1 complete pack before moving onto the next. This system compels the resuscitation team to provide a balanced ratio of product, rather than transfusing based on delayed laboratory results or personal sentiment. In addition to ensuring that patients receive hemostatic ratios, this strategy removes a responsibility from the numerous demands already placed on resuscitation teams as they multitask through the resuscitations, providing a secondary benefit to patients by allowing the teams to focus instead on other important tasks.

INTENSIVE CARE UNIT RESUSCITATION

In general, hemorrhage sufficient to warrant an MT requires ICU admission. Arrival of these patients to the ICU marks an important checkpoint or node in the patient's care and should prompt a review of the resuscitative efforts so far and a plan and direction for further care. In addition to addressing factors that exacerbate coagulopathy, including hypothermia, acidosis, and hypocalcemia, clinicians should ask whether the patient is still receiving MTP or whether the patient has been transitioned to laboratory-directed resuscitation. An appropriate laboratory-directed algorithm should be in place, and care at this point should be guided according to these assays. If an active MTP is still required, clinicians should ask whether the patient warrants a return to the operating room. If not, blood pressures targets may be returned to normal and supportive or maintenance fluids begun. However, should the patient's abdomen remain open, substituting hypertonic saline for maintenance fluids (rather than standard crystalloids) should be considered to reduce bowel wall and mesenteric edema.[79]

With respect to continued high ratios of plasma and platelets, the PROMMTT (Prospective, Observational, Multicenter, Major Trauma Transfusion) study provided answers to this question.[80] This prospective cohort study found that higher (1:1:1) ratios of plasma and platelet to RBC decreased patient mortality during the first

6 hours. However, the investigators noted that, after 6 hours (and continuing through 30 days), although higher ratios were not associated with increased complications they were also of no benefit.

RETURN TO WHOLE BLOOD

The reasons for a shift away from whole-blood transfusion were many. With advances in blood banking, fractionation provided a means by which components specific to the needs of the patient, including patients without trauma, could be provided without having to administer whole blood. Furthermore, blood banking provided a means by which some components could be stored for extended durations, thereby decreasing concerns about a limited and time-sensitive supply. As a result, whole blood was removed as an available product. However, this was done without consideration of whether whole blood was more or less superior to component therapy in the resuscitation of hemorrhaging patients. In 2013, Cotton and colleagues[81] challenged the assumption that component therapy was equal to whole blood by completing a pilot randomized controlled trial. They discovered that the use of modified whole blood did not decrease transfusion volumes compared with component therapy. However, when patients with severe brain injuries were excluded, the remaining patients receiving modified whole blood required less volume of transfusion than those receiving component therapy. Of note, the modified whole-blood group required the additional transfusion of platelets at a ratio equivalent to the component therapy group. This work suggests that the use of whole blood may lead to similar survival outcomes as component therapy but with a decrease in the volume of transfusion required to achieve this goal. Further work by the Early Whole Blood Investigators has found that patients transfused with modified whole blood compared with component therapy showed improved thrombin potential and platelet aggregation.[82] This area requires further study. The use of fresh whole blood is likely to continue in the military setting because it has been found to be convenient, safe, and effective.[83]

SUMMARY

Balanced resuscitation has become a key tenet in the care of patients with trauma. The implementation of this central strategy has been associated with reduced death from major bleeding, decreasing reported mortalities from more than 60% in 2007 to as low as 20% currently. During this time, clinicians have begun to appreciate that aggressive crystalloid resuscitation leads to significant clinical complications and harm and that massive fluid resuscitation should be avoided. The use of crystalloids and colloids should be as thoughtful and careful as with any medication. When the limitation of crystalloid resuscitation is combined with permissive hypotension, prevention of hypothermia, and the transfusion of component blood into ratios that match the composition of whole blood early in the care of patients with trauma, outcomes are significantly improved. Balanced resuscitation provides an early means to treat trauma-induced coagulopathy, leads to an overall decrease in the use of blood products, and improves patient survival. Although further advances in the resuscitation strategies used to treat patients with trauma will be made and improvements in patient-specific targeting of transfusions will be developed, there is little doubt that balanced resuscitation using modern MTPs is likely here to stay. Bleeding needs blood to stop bleeding.

REFERENCES

1. Cothren CC, Moore EE, Hedegaard HB, et al. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. World J Surg 2007; 31(7):1507–11.
2. Centers for Disease Control and Prevention. Web-based injury statistics query and reporting system. Atlanta (GA): US Department of Health and Human Services, CDC, National Center for Injury Prevention and Control; 2003.
3. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38(2):185–93.
4. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg 1998;186(5):528–33.
5. Rhee P, Joseph B, Pandit V, et al. Increasing trauma deaths in the United States. Ann Surg 2014;260(1):13–21.
6. Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. World J Surg 2007;31(5):1055–64.
7. American College of Surgeons Committee on Trauma. ATLS, advanced trauma life support student course manual. 9th edition. Chicago: American College of Surgeons; 2012.
8. ATLS Subcommittee, American College of Surgeons' Committee on Trauma, International ATLS Working Group. Advanced trauma life support (ATLS®): the ninth edition. J Trauma 2013;74(5):1363–6.
9. Cinat ME, Wallace WC, Nastanski F, et al. Improved survival following massive transfusion in patients who have undergone trauma. Arch Surg 1999;134(9): 964–8.
10. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015;313(5):471–82.
11. Hess JR, Thomas MJ. Blood use in war and disaster: lessons from the past century. Transfusion 2003;43(11):1622–33.
12. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. J Trauma 2003;54(5S):S46–51.
13. Sullivan MT, Cotten R, Read EJ, et al. Blood collection and transfusion in the United States in 2001. Transfusion 2007;47(3):385–94.
14. Dumont LJ, AuBuchon JP. Evaluation of proposed FDA criteria for the evaluation of radiolabeled red cell recovery trials. Transfusion 2008;48(6):1053–60.
15. Downes KA, Wilson E, Yomtovian R, et al. Serial measurement of clotting factors in thawed plasma stored for 5 days. Transfusion 2001;41(4):570.
16. Hess JR. Conventional blood banking and blood component storage regulation: opportunities for improvement. Blood Transfus 2010;8(S3):S9–15.
17. Counts RB, Haisch C, Simon TL, et al. Hemostasis in massively transfused trauma patients. Ann Surg 1979;190(1):91–9.
18. Carrico CJ, Canizaro PC, Shires GT. Fluid resuscitation following injury: rationale for the use of balanced salt solutions. Crit Care Med 1976;4(2):46–54.
19. Picard A. The gift of death: confronting Canada's tainted-blood tragedy. Toronto: HarperCollins; 1995.
20. Meier, B. Blood, money and aids: haemophiliacs are split; liability cases bogged down in disputes. The New York Times. June 11, 1996.
21. Farion KJ, McLellan BA, Boulanger BR, et al. Changes in red cell transfusion practice among adult trauma victims. J Trauma 1998;44(4):583–7.

22. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961;154(5):803–10.
23. Virtue RW, LeVine DS, Aikawa JK. Fluid shifts during the surgical period: RISA and s^{35} determinations following glucose, saline or lactate infusion. Ann Surg 1966;163(4):523–8.
24. Nielsen OM, Engell HC. The importance of plasma colloid osmotic pressure for interstitial fluid volume and fluid balance after elective abdominal vascular surgery. Ann Surg 1986;203(1):25–9.
25. Moore FD, Shires GT. Moderation. Ann Surg 1967;166(2):300–1.
26. Shoemaker WC, Appel P, Bland R. Use of physiologic monitoring to predict outcome and to assist in clinical decisions in critically ill postoperative patients. Am J Surg 1983;146(1):43–50.
27. Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. J Trauma 1993;35(4):584–8.
28. Stone HH, Strom PR, Mullins RJ. Management of the major coagulopathy with onset during laparotomy. Ann Surg 1983;197(5):532–5.
29. Rotondo MF, Schwab CW, McGonigal MD, et al. 'Damage control': an approach for improved survival in exsanguinating penetrating abdominal injury. J Trauma 1993;35(3):375–82.
30. Fietsam R Jr, Villalba M, Glover JL, et al. Intra-abdominal compartment syndrome as a complication of ruptured abdominal aortic aneurysm repair. Am Surg 1989; 55(6):396–402.
31. Bendahan J, Coetzee CJ, Papagianopoulos C, et al. Abdominal compartment syndrome. J Trauma 1995;38(1):152–3.
32. Scheingraber S, Rehm M, Sehmisch C, et al. Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999;90(5):1265–70.
33. Williams EL, Hildebrand KL, McCormick SA, et al. The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers. Anesth Analg 1999;88(5):999–1003.
34. Takil A, Eti Z, Irmak P, et al. Early postoperative respiratory acidosis after large intravascular volume infusion of lactated ringer's solution during major spine surgery. Anesth Analg 2002;95(2):294–8.
35. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. Chest 1999;115(5):1371–7.
36. Wiedemann HP, Wheeler AP, Bernard GR, et al, National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564–75.
37. Richard C, Warszawski J, Anguel N, et al, French Pulmonary Artery Catheter Study Group. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. JAMA 2003;290(20):2713–20.
38. Sandham JD, Hull RD, Brant RF, et al, Canadian Critical Care Clinical Trials Group. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 2003;348(1):5–14.
39. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 2002;359(9320):1812–8.
40. Lamke LO, Liljedahl SO. Plasma volume expansion after infusion of 5%, 20% and 25% albumin solutions in patients. Resuscitation 1976;5(2):85–92.

41. Tønnessen T, Tølløfsrud S, Kongsgaard UE, et al. Colloid osmotic pressure of plasma replacement fluids. Acta Anaesthesiol Scand 1993;37(4):424–6.
42. Robless P, Okonko D, Mikhailidis DP, et al. Dextran 40 reduces in vitro platelet aggregation in peripheral arterial disease. Platelets 2004;15(4):215–22.
43. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis. JAMA 2013;309(7):678–88.
44. Fenger-Eriksen C, Tønnesen E, Ingerslev J, et al. Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. J Thromb Haemost 2009;7(7):1099–105.
45. Schramko AA, Suojaranta-Ylinen RT, Kuitunen AH, et al. Rapidly degradable hydroxyethyl starch solutions impair blood coagulation after cardiac surgery: a prospective randomized trial. Anesth Analg 2009;108(1):30–6.
46. Traverso LW, Medina F, Bolin RB. The buffering capacity of crystalloid and colloid resuscitation solutions. Resuscitation 1985;12(4):265–70.
47. Ketchum L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate, and platelet transfusion in trauma. J Trauma 2006;60(6S):S51–8.
48. Pati S, Matijevic N, Doursout MF, et al. Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. J Trauma 2010;69(S1):S55–63.
49. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 2007;131(5):1308–14.
50. Robinson BR, Cotton BA, Pritts TA, et al. Application of the Berlin definition in PROMMTT patients: the impact of resuscitation on the incidence of hypoxemia. J Trauma 2013;75(1S):S61–7.
51. Kozar RA, Peng Z, Zhang R, et al. Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. Anesth Analg 2011;112(6):1289–95.
52. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007;62(2):307–10.
53. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. J Trauma 2006;60(6 Suppl):S91–6.
54. Ho AM, Karmakar MK, Dion PW. Are we giving enough coagulation factors during major trauma resuscitation? Am J Surg 2005;190(3):479–84.
55. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248(3):447–58.
56. Gunter OL Jr, Au BK, Isbell JM, et al. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 2008;65(3):527–34.
57. Cannon JW, Khan MA, Raja AS, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma 2017;82(3):605–17.
58. Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. Br J Anaesth 2015;115(1):76–83.
59. Haut ER, Kalish BT, Cotton BA, et al. Prehospital intravenous fluid administration is associated with higher mortality in trauma patients: a National Trauma Data Bank analysis. Ann Surg 2011;253(2):371–7.

60. Cotton BA, Jerome R, Collier BR, et al, Eastern Association for the Surgery of Trauma Practice Parameter Workgroup for Prehospital Fluid Resuscitation. Guidelines for prehospital fluid resuscitation in the injured patient. J Trauma 2009;67(2):389–402.
61. Schreiber MA, Meier EN, Tisherman SA, et al, ROC Investigators. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma 2015;78(4):687–95.
62. Cannon WB, Fraser J, Cowell EM. The preventive treatment of wound shock. JAMA 1918;70:618–21.
63. Beecher HK. Preparation of battle casualties for surgery. Ann Surg 1945;21: 769–92.
64. Beecher HK. Resuscitation and anesthesia for wounded men. Springfield (IL): Banerstone House; 1949.
65. Holcomb JB, Donathan DP, Cotton BA, et al. Prehospital transfusion of plasma and red blood cells in trauma patients. Prehosp Emerg Care 2015;19(1):1–9.
66. Kim BD, Zielinski MD, Jenkins DH, et al. The effects of prehospital plasma on patients with injury: a prehospital plasma resuscitation. J Trauma 2012;73(2 Suppl 1):S49–53.
67. Brown JB, Sperry JL, Fombona A, et al. Pre-trauma center red blood cell transfusion is associated with improved early outcomes in air medical trauma patients. J Am Coll Surg 2015;220(5):797–808.
68. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009;66(2):346–52.
69. Goodman MD, Hawes HG, Pommerening MJ, et al. Prehospital ABC score accurately triages patients who will require immediate resource utilization. Presented at the 72nd Annual Meeting of AAST and Clinical Congress of Acute Care Surgery. San Francisco, CA, September 18–21, 2013.
70. Parimi N, Hu PF, Mackenzie CF, et al. Automated continuous vital signs predict use of uncrossed matched blood and massive transfusion following trauma. J Trauma 2016;80(6):897–906.
71. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994; 331(17):1105–9.
72. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002;52(6):1141–6.
73. Cantle PM, Cotton BA. Prediction of massive transfusion in trauma. Crit Care Clin 2017;33(1):71–84.
74. Radwan ZA, Bai Y, Matijevic N, et al. An emergency department thawed plasma protocol for severely injured patients. JAMA Surg 2013;148(2):170–5.
75. Matijevic N, Wang YW, Cotton BA, et al. Better hemostatic profiles of never-frozen liquid plasma compared with thawed fresh frozen plasma. J Trauma 2013;74(1): 84–90.
76. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. Ann Surg 2011;254(4):598–605.
77. Morrison CA, Carrick MM, Norman MA, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. J Trauma 2011;70(3):652–63.

78. Duke MD, Guidry C, Guice J, et al. Restrictive fluid resuscitation in combination with damage control resuscitation: time for adaptation. J Trauma 2012;73(3):674–8.
79. Harvin JA, Mims MM, Duchesne JC, et al. Chasing 100%: the use of hypertonic saline to improve early, primary fascial closure after damage control laparotomy. J Trauma 2013;74(2):426–30.
80. Holcomb JB, del Junco DJ, Fox EE, et al, PROMMTT Study Group. The Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013;148(2):127–36.
81. Cotton BA, Podbielski J, Camp E, et al, Early Whole Blood Investigators. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Ann Surg 2013;258(4):527–32.
82. Rahbar E, Cardenas JC, Matijevic N, et al, Early Whole Blood Investigators. Trauma, time, and transfusions: a longitudinal analysis of coagulation markers in severely injured trauma patients receiving modified whole blood or component blood products. Shock 2015;44(5):417–25.
83. Kauvar DS, Holcomb JB, Norris GC, et al. Fresh whole blood transfusion: a controversial military practice. J Trauma 2006;61(1):181–4.

CRITICAL CARE

VIEWPOINT

A balanced view of balanced solutions

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Abstract

The present review of fluid therapy studies using balanced solutions versus isotonic saline fluids (both crystalloids and colloids) aims to address recent controversy in this topic. The change to the acid–base equilibrium based on fluid selection is described. Key terms such as dilutional-hyperchloraemic acidosis (correctly used instead of dilutional acidosis or hyperchloraemic metabolic acidosis to account for both the Henderson–Hasselbalch and Stewart equations), isotonic saline and balanced solutions are defined. The review concludes that dilutional-hyperchloraemic acidosis is a side effect, mainly observed after the administration of large volumes of isotonic saline as a crystalloid. Its effect is moderate and relatively transient, and is minimised by limiting crystalloid administration through the use of colloids (in any carrier). Convincing evidence for clinically relevant adverse effects of dilutional-hyperchloraemic acidosis on renal function, coagulation, blood loss, the need for transfusion, gastrointestinal function or mortality cannot be found. In view of the long-term use of isotonic saline either as a crystalloid or as a colloid carrier, the paucity of data documenting detrimental effects of dilutional-hyperchloraemic acidosis and the limited published information on the effects of balanced solutions on outcome, we cannot currently recommend changing fluid therapy to the use of a balanced colloid preparation.

Introduction

Normal saline solution has been used for over 50 years in a multitude of clinical situations as an intraoperative, resuscitation and maintenance fluid therapy. Neither normal nor physiological, however, saline solution is still a standard against which other solutions are measured. Much attention has been given recently to so-called balanced solutions such as Ringer's lactate, and more recent derivatives. Colloids prepared in balanced electrolyte solutions have also been developed, alongside colloids in isotonic saline.

As one might expect, excessive use of saline has been observed to result in hyperchloraemic acidosis – which has been identified as a potential side effect of saline-based solutions. There is debate about the morbidity associated with this condition, although some consider the associated morbidity is probably low. It has been suggested that the use of balanced solutions may avoid this effect.

This acidosis effect was reviewed and highlighted in the British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients [1]. These guidelines clearly recommend the use of balanced crystalloids rather than saline – but they make no specific recommendations regarding colloids, implying that they could be either standard or balanced. The publication of these guidelines has provoked strong reactions. In a *British Medical Journal* editorial, Liu and Finfer comment: 'Although administration of normal saline can cause hyperchloraemic acidosis, we do not know whether this is harmful to patients. Adopting this guideline is unlikely to harm patients, but may not have any tangible benefit' [2].

Others have reviewed the physiological effects of acidosis. Handy and Soni noted that 'There is little evidence that in 50 years of normal saline usage, there has been significant morbidity from the use of this fluid' [3]. Liu and Finfer continue: 'The danger in providing consensus guidelines endorsed by specialist societies is that clinicians may feel pressured to adopt interventions that may, in the longer term, be found to cost more and to do more harm than good. We agree with the recently expressed view that unless recommendations are based on high quality primary research, then perhaps guidelines should be avoided completely, and clinicians would be better off making clinical decisions on the basis of primary data' [4].

Given the obvious controversy that exists based on the interpretation of the available information, the entire topic should clearly be reviewed again. Accordingly, the present article reviews the available literature comparing

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balanced solutions with isotonic saline fluids (both crystalloids and colloids) and investigates the scientific basis that should be taken into account in any future guidelines or recommendations.

The acid–base equilibrium: Henderson–Hasselbalch versus Stewart

It is vital to determine the mechanism for an acid–base disturbance in critically ill patients in order to administer appropriate treatment. The Henderson–Hasselbalch equation is still the standard method for interpreting acid–base equilibrium in clinical practice [5]:

$$pH = pK_1' + \log[HCO_3^-] / (S \times PCO_2)$$

This equation describes how plasma CO_2 tension, plasma bicarbonate (HCO_3^-) concentration, the apparent dissociation constant for plasma carbonic acid (pK) and the solubility of CO_2 in plasma interact to determine plasma pH. The magnitude of the metabolic acidosis is generally quantified by the base deficit or base excess, which is defined as the amount of base (or acid) that must be added to a litre of blood to return the pH to 7.4 at a partial pressure of carbon dioxide (PCO_2) of 40 mmHg. The main consequence of infusion of isotonic saline is a dilution of bicarbonate. The dilution of albumin may also play a minor role. Accordingly, the observed disorder is reported as a dilutional acidosis, associating a base deficit with a high chloride concentration.

A different approach (the strong ion approach) to acid–base equilibrium was developed in 1983 by Stewart to account for fluctuation of the variables that independently regulate plasma pH [6]. He proposed that plasma pH is affected by three independent factors: PCO_2; the strong ion difference (SID), which is the difference between the charge of plasma strong cations (sodium, potassium, magnesium and calcium) and strong anions (chloride, sulphate, lactate and others); and the sum of all anionic charges of weak plasma acids (A_{tot}), which is the total plasma concentration of nonvolatile buffers (albumin, globulins, phosphate). More advanced explanations are available in a recent review by Yunos and colleagues [7]. The Stewart equation may be written in a similar form to the Henderson–Hasselbalch equation [8]:

$$pH = pK_1' + \log[SID - A_{tot} / (1 + 10^{(pKa - pH)})] / (S \times PCO_2)$$

At the usual pH of plasma, part of the albumin complex carries a negative charge, which could therefore play a role in buffering H^+ ions. The same applies to phosphate, although the concentration of phosphate in the plasma is too low to provide significant buffering. Accordingly, the Stewart approach emphasises the role of albumin, phosphate and other buffers in acid–base equilibrium. The Stewart approach can distinguish six primary acid–base disturbances instead of the four differentiated by the Henderson–Hasselbalch equation. This strong ion approach also provides a more comprehensive explanation of the role of chloride in acid–base equilibrium.

The SID of isotonic saline being 0, the infusion of large quantities will dilute the normal SID of plasma and decrease pH. Hyperchloraemic metabolic acidosis is therefore a decrease in SID associated with an increase in chloride. The Stewart equation also shows that the infusion of isotonic saline will also dilute albumin and decrease A_{tot}, which tends to increase pH. Using the Stewart equation, a balanced solution with a physiological SID of 40 mEq/l would induce a metabolic alkalosis. Morgan and Venkatesh have calculated that a balanced solution should have a SID of 24 mEq/l in order to avoid this induction [9]. It should be noted that balanced solutions using organic anions (such as lactate, acetate, gluconate, pyruvate or malate) have an *in vitro* SID equal to 0, similar to isotonic saline. *In vivo*, the metabolism of these anions increases the SID and also decreases the osmolarity of the solution.

This equation, while comprehensive, is still complex for common use if used in its entirety, but a simplified Stewart approach can be used to make a graphical interpretation of the acid–base equilibrium. This approach takes into account the effects of the most important substances affecting equilibrium: sodium, potassium, calcium and magnesium minus chloride and lactate. In this approach, the apparent SID is defined as follows (see Figure 1):

$$\text{Apparent SID} = ([Na^+] + [K^+]) - ([Cl^-] + [\text{lactate}])$$

The two acid–base equilibrium approaches are mathematically equivalent but are completely different from a conceptual point of view. Both are subject to criticism. The Stewart approach has been criticised for incorporating bicarbonate as a dependent variable, the result of a calculation, while it is obvious that physiologically bicarbonate plays a central role and is regulated mainly by the kidneys. Conversely, the Henderson–Hasselbalch approach is centred on bicarbonate, which may reflect the physiological reality better. In the dilution concept, metabolic acidosis following resuscitation with large volumes of isotonic saline is attributed to dilution of serum bicarbonate. The Stewart approach rejects this explanation, however, and offers an alternative that is based on a decrease in SID. This mechanistic explanation is questioned by several authors for fundamental chemical reasons [10,11]. If correct, the Stewart approach is valid at the mathematical level but does not provide mechanistic insights. The quantification and categorisation of acid–base disorders using the Stewart approach,

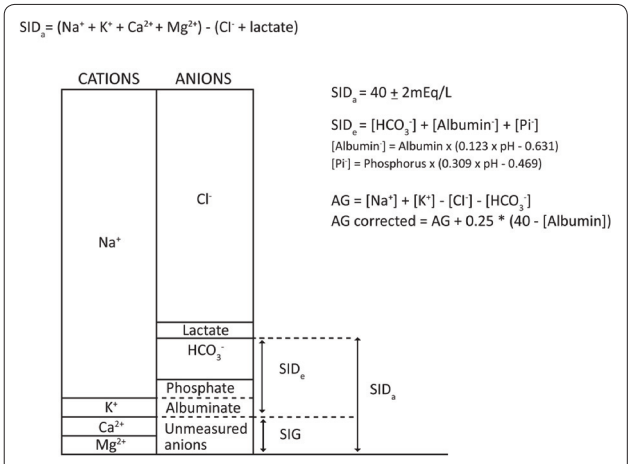

Figure 1. Representation of the Stewart model. Charge balance in blood plasma. Any difference between apparent strong ion difference (SID_a) and effective strong ion difference (SID_e) is the strong ion gap (SIG) and presents unmeasured anions. The SIG should not be confused with the anion gap (AG). A corrected AG can be calculated to account for variations in albumin concentration. Adapted from Stewart [6].

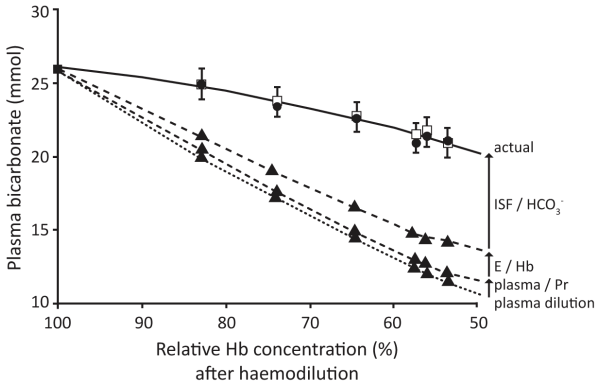

Figure 2. Plasma bicarbonate concentration versus relative haemoglobin after acute haemodilution in different patient groups. Plasma bicarbonate (HCO_3^-) concentration (mmol/l) versus relative haemoglobin (Hb) (%) after acute normovolaemic haemodilution in different patient groups. Comparison is shown for predicted (open squares) and reported (filled circles) values [18] of the actual HCO_3^- concentration (top curve), composed of the calculated HCO_3^- values (filled triangles) from plasma dilution, plus the increments from the plasma proteins (Pr), the erythrocytes (E), and the interstitial fluid (ISF) with corresponding buffers. Adapted from Lang and Zander [12].

however, may be helpful in clinical practice to understand some complex disorders.

The intra-erythrocyte and interstitial space buffers are not taken into account in either approach. These buffers play a major role in acid–base equilibrium and must be included, particularly in the case of isotonic saline administration [12] (Figure 2).

The most important consideration is the cause of the acidosis. Acidosis is often the consequence of a physiological disturbance or an iatrogenic event. The difficulty lies in separating the effects of the pathophysiology driving the acidosis. For example, metabolic acidosis can be a sign of organ distress due to hypoperfusion or hypoxia (for example, shock, ketoacidosis or kidney disease) [3]. This will produce profound physiological effects that are all readily ascribed to the acidosis rather than to its cause. Correction of the pathology may correct the acidosis, but correction of the acidosis solely is unlikely to affect the pathology. Therefore it is important to understand the mechanism causing the acidosis.

Definitions

In the present article, in an attempt to better describe disorders and solutions, we have used the following terms.

Dilutional-hyperchloraemic acidosis

The term dilutional-hyperchloraemic acidosis is used instead of dilutional acidosis or hyperchloraemic metabolic acidosis, in order to reconcile both theories (Henderson–Hasselbalch and Stewart). In reality, many articles on hyperchloraemic metabolic acidosis do not report SID changes and only mention base excess variations and chloride concentrations.

Isotonic saline

Isotonic saline describes the main property of 0.9% saline solution. The solution is neither normal, abnormal nor unbalanced. Sodium and chloride are partially active, the osmotic coefficient being 0.926. The actual osmolality of 0.9% saline is 287 mOsm/kg H_2O, which is exactly the same as the plasma osmolality.

Balanced solutions

Used generally to describe different solutions with different electrolyte compositions close to plasma composition, balanced solutions are neither physiological nor plasma-adapted. Table 1 presents the electrolyte composition of commonly available crystalloids. Table 2 presents the electrolyte composition of commonly used colloids.

Quantitative effects of isotonic saline infusion on acid–base equilibrium

The effects of isotonic saline infusion are illustrated by Rehm and Finsterer in patients awaiting intra-abdominal surgery [13]. Patients received 40 ml/kg/hour of 0.9% isotonic saline, a total of 6 litres isotonic saline in 2 hours. The apparent SID decreased from 40 to 31 mEq/l, chloride significantly increased from 105 to 115 mmol/l and a decrease in base excess of approximately 7 mmol/l was observed. These data perfectly illustrate

Table 1. Electrolyte composition (mmol/l) of commonly available crystalloids

Electrolyte	Plasma	0.9% NaCl	Ringer's lactate, Hartmann's	Plasma-Lyte®	Sterofundin®
Sodium	140	154	131	140	140
Potassium	5	0	5	5	4
Chloride	100	154	111	98	127
Calcium	2.2	0	2	0	2.5
Magnesium	1	0	1	1.5	1
Bicarbonate	24	0	0	0	0
Lactate	1	0	29	0	0
Acetate	0	0	0	27	24
Gluconate	0	0	0	23	0
Maleate	0	0	0	0	5

Plasma-Lyte® from Baxter International (Deerfield, IL, USA). Sterofundin® from B Braun (Melsungen, Germany).

Table 2. Electrolyte composition (mmol/l) of commonly available colloids

	Albumin 4%	Plasmion® Geloplasma®	Gelofusine®	Voluven® (waxy maize HES 6% 130/0.40)	Venofundin® (potato HES 6% 130/0.42)	Hextend® (waxy maize HES 6% 670/0.75)	Volulyte® (waxy maize HES 6% 130/0.40)	PlasmaVolume® (potato HES 6% 130/0.42)	Tetraspan® (potato HES 6% 130/0.42)
Sodium	140	150	154	154	154	143	137	130	140
Potassium	0	5	0	0	0	3	4	5.4	4.0
Chloride	128	100	125	154	154	124	110	112	118
Calcium	0	0	0	0	0	2.5	0	0.9	2.5
Magnesium	0	1.5	0	0	0	0.5	1.5	1	1.0
Bicarbonate	0	0	0	0	0	0	0	0	0
Lactate	0	30	0	0	0	28	0	0	0
Acetate	0	0	0	0	0	0	34	27	24
Malate	0	0	0	0	0	0	0	0	5
Octanoate	6.4	0	0	0	0	0	0	0	0

HES, hydroxyethyl starch. Gelofusine®, Venofundin® and Tetraspan® from B Braun (Melsungen, Germany). Plasmion®, Geloplasma®, Voluven® and Volulyte® from Fresenius-Kabi (Bad Homburg, Germany). Hextend® from BioTime Inc. (Berkeley, CA, USA). PlasmaVolume® from Baxter International (Deerfield, IL, USA).

dilutional-hyperchloraemic acidosis following infusion of large volumes of isotonic saline in clinical practice. Before determining the clinical relevance of dilutional hyperchloraemic acidosis, it is important to quantify the respective contribution of crystalloids and colloids.

Several studies have reported the biological effects following infusion of crystalloids alone [14,15]. Boldt and colleagues provide an interesting illustration of the effects following infusion of very high doses of crystalloid (isotonic saline versus Ringer's lactate) [16]. In patients undergoing major abdominal surgery, they reported the intraoperative infusion of 8 litres of crystalloids, followed by a further 10 litres of postoperative infusion in 48 hours (Table 3), resulting in a total dose of 18 litres of either Ringer's lactate or isotonic saline. As shown in Table 3, these extreme doses of isotonic saline were associated with moderate and transient effects on acid–base equilibrium: a decrease in base excess of 5 mmol/l that lasted for 1 or 2 days.

A number of studies have also reported and compared the effects following the infusion of large volumes of colloids and crystalloids with isotonic saline or balanced solutions [17-22].

In patients undergoing abdominal surgery, Boldt and colleagues used colloid (HES 130/0.42) either in a balanced solution or in an isotonic saline solution. In this study, a total balanced fluid therapy (colloid and crystalloid) was compared with a total isotonic saline-based strategy [18]. It is interesting to note that, despite the large volumes of fluid used (>6 litres), the difference in chloride concentration was +8 mmol/l and the difference in base excess was –5 mmol/l between the groups (Table 4). These changes were similar to or lower than those in other studies (Table 4).

O'Dell and colleagues established that there is an inverse linear relationship between chloride load and base excess [23]. According to this relationship, to decrease base excess by 10 mmol/l in a typical 70 kg

Table 3. Total volume input and urine output: effects on chloride and base excess [16]

	After surgery	5 hours on ICU	First postoperative day	Second postoperative day (total)
Cumulative volume input (ml)				
Ringer's lactate	7,950 ± 950	9,070 ± 920	14,150 ± 1,150	18,750 ± 1,890
Saline solution	8,230 ± 580	9,550 ± 880	13,790 ± 1,650	17,990 ± 1,790
Cumulative urine output (ml)				
Ringer's lactate	1,950 ± 340	4,400 ± 410	7,700 ± 370	11,450 ± 460
Saline solution	2,250 ± 240	3,920 ± 350	6,950 ± 430	12,940 ± 390
Cl^- (mmol/l)				
Ringer's lactate	104 ± 3	105 ± 3	102 ± 2	102 ± 3
Saline solution	113 ± 4*†	111 ± 3*†	111 ± 3*†	106 ± 5
Base deficit (mmol/l)				
Ringer's lactate	–0.5 ± 0.6	–1.0 ± 1.2	2.0 ± 0.5	2.9 ± 1.1
Saline solution	–5.6 ± 2.1*†	–4.2 ± 1.9*†	–2.8 ± 1.1*†	0.3 ± 1.5*

ICU, intensive care unit. *P <0.05 difference compared with the other group. †P <0.05 difference compared with baseline values.

patient it would be necessary to infuse 20 mmol/kg chloride – equivalent to around 9 litres of isotonic saline. Putting this in the context of the normal maximum doses of colloids, infusion of 50 ml/kg HES 130/0.4 would reduce base excess by a maximum of 3.5 mmol/l, which largely corresponds with observations in published studies. Overall, these studies suggest that when patients are treated with a combination of isotonic saline-based colloids and crystalloids, the effects on acid–base equilibrium are limited.

Base and colleagues used a different fluid strategy in patients undergoing cardiac surgery. HES 130/0.4 was administered either in a balanced solution or a saline solution. The two groups also received the same balanced crystalloid, Ringer's lactate [17]. The chloride concentration at the end of surgery was 110 mmol/l in the group receiving HES in a balanced solution, compared with 112 mmol/l in the isotonic saline-based solution. The difference is statistically significant but is not clinically relevant. Base excess decreased in both groups, but the maximum difference between the groups at any time point was around 2 mmol/l.

The respective role of crystalloids and colloids on acid–base equilibrium is perfectly illustrated by Boldt and colleagues in elderly patients undergoing abdominal surgery [24]. Three different strategies were used: Ringer's lactate, isotonic saline, and HES 130/0.4 plus Ringer's lactate. The chloride and sodium loads and the effect on base excess are shown in Figure 3. Although the colloid used in this study was supplied in an isotonic saline carrier, overall the impact on base excess was similar to that of Ringer's lactate alone and remained within the normal range.

Overall, these studies suggest that large volumes of saline will increase the chloride concentration and reduce base excess in a dose-dependent manner, with the peak effect occurring a few hours post infusion. The effect is temporary, and levels generally return to normal within 1 or 2 days. When fluid therapy is based on colloids in an isotonic saline carrier, together with a balanced crystalloid like Ringer's lactate, the effects on acid–base equilibrium appear limited. Owing to a lack of published clinical experience, it remains to be seen whether patients with pre-existing metabolic acidosis are more affected due to a reduced buffering capacity. Transient isotonic saline-induced reduction of base excess should be considered when interpreting the acid–base status in unstable patients.

Is dilutional-hyperchloraemic acidosis clinically relevant?

While it is clear that dilutional-hyperchloraemic acidosis exists, it is important to examine whether it has any effect on organ function. The kidney, gastrointestinal tract and coagulation system have often been mentioned as possible targets.

Effects of dilutional-hyperchloraemic acidosis on renal function

Animal studies suggest that chloride may have effects on the kidney including renal vasoconstriction, an increase in renal vascular resistance, a decrease in glomerular filtration rate and a decrease in renin activity [25-28]. At normal and slightly high concentrations, however, the effects are small [29].

Differences in osmolarity between Ringer's lactate and isotonic saline have to be taken into account to understand the effects on renal function and urine output. The osmolarity of Ringer's lactate is 273 mOsm/l. In dilute physiological solutions, the values of osmolality

Table 4. Effects on base excess and chloride concentrations from different clinical studies

Study	Setting	Infusion strategy	Volumes infused during study period (ml)	Minimal value in base excess (mmol/l)	Maximal change in chloride (mmol/l)
Boldt and colleagues [18]	Abdominal surgery	Balanced group		<1[a]	+3[a]
		HES 130/0.42	3,866 ± 1,674		
		Modified RL	5,966 ± 1,202		
		Saline-based group		–5[a]	+8[a]
		HES 130/0.42	3,533 ± 1,302		
		Isotonic saline	5,333 ± 1,063		
Kulla and colleagues [21]	Abdominal surgery	Balanced		–1.8	+3
		HES 130/0.42	1,923 ± 989		
		Modified RL	4,268 ± 999		
		Saline-based		–4.2	+5
		HES 130/0.42	1,828 ± 522		
		Modified saline	4,490 ± 1,126		
Boldt and colleagues [19]	Cardiac surgery	Balanced		–1.2	Not reported
		HES 130/0.42	2,750 ± 640		
		Modified RL	5,200 ± 610		
		Saline-based		–4.4	Not reported
		HES 130	2,820 ± 550		
		Isotonic saline	5,150 ± 570		
Boldt and colleagues [20]	Cardiopulmonary bypass	Balanced		0[a]	Not reported
		HES 130/0.42	3,090 ± 540		
		Modified RL	4,010 ± 410		
		Saline-based		–6[a]	Not reported
		5% albumin	3,110 ± 450		
		Isotonic saline	5,450 ± 560		
Boldt and colleagues [22]	Cardiopulmonary bypass	Balanced		–1[a]	Not reported
		HES 130/0.40	2,950 ± 530		
		Modified RL	5,090 ± 750		
		Saline-based		–5[a]	Not reported
		5% albumin	3,050 ± 560		
		Isotonic saline	5,050 ± 680		

HES, hydroxyethyl starch; RL, Ringer's lactate. [a]Values estimated from figures reported in the article.

and osmolarity are interchangeable. *In vivo*, however, the osmolality of Ringer's lactate is only 254 mOsm/kg. This discrepancy is due to incomplete ionisation of the solutes in Ringer's lactate. On the contrary, isotonic saline, which is completely ionised, has an osmolality similar to the calculated osmolarity of 308 mOsm/l. Compared with the osmolality of normal serum (285 to 295 mOsm/kg), therefore, Ringer's lactate is clearly hypotonic while 0.9% saline is isotonic.

In a study with human volunteers, Williams and colleagues tested the hypothesis that infusion of large volumes of Ringer's lactate or isotonic saline may have different effects on renal function and urine output [15]. There was a significant difference in mean time to urination, Ringer's lactate solution being associated with the shorter time to first urine output. In fact, in the Ringer's lactate group a decrease in serum osmolality probably inhibited the release of antidiuretic hormone. The resulting diuresis of hypotonic urine causes the serum osmolality to return quickly to normal.

These changes in osmolarity must be taken into account in the interpretation of clinical studies comparing Ringer's lactate with isotonic saline. In a similar study by Reid and colleagues, time to first micturition was shorter in the Ringer's lactate group, and was associated with a decreased urine osmolarity [30]. This suggests that the

Group	Chloride load in mmol (% vs isotonic saline)	Sodium load in mmol (% vs isotonic saline)
Isotonic saline	1571 (100%)	1571 (100%)
Ringer's Lactate	1106 (70%)	1313 (84%)
HES 130/0.4 plus Ringer's Lactate	745 (47%)	804 (51%)

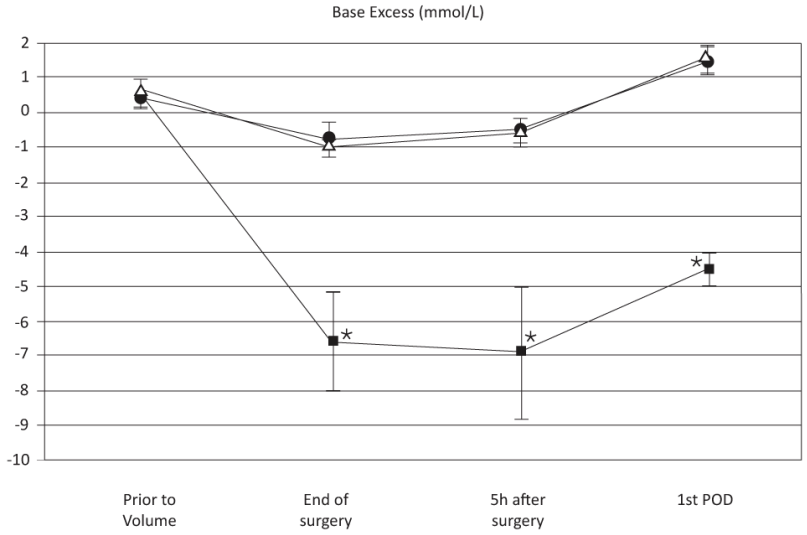

Figure 3. Chloride load and base excess in elderly patients undergoing abdominal surgery. Chloride load in the three groups of patients – Ringer's lactate group (filled circles), isotonic saline group (filled squares), and HES 130/0.4 plus Ringer's lactate (open triangles) – was calculated. The variations in base excess for the three groups are shown graphically. It is remarkable that there is no difference between the Ringer's lactate group and the HES 130/0.4 plus Ringer's lactate group. *P <0.05. POD, postoperative day. Adapted from Boldt and colleagues [24].

free water clearance adjusted to changes in osmolality. In their study, the isotonic saline group retained a greater proportion of the sodium load than did the Ringer's lactate group, which may account for the difference in fluid retention. These results emphasise that differences in osmolality between balanced solutions and isotonic saline must be taken into account in the interpretation of renal function parameters such as time to micturition and urine output.

O'Malley and colleagues compared Ringer's lactate with isotonic saline in patients undergoing renal transplantation. This study found that recipients undergoing kidney transplants had greater acidosis and higher potassium concentrations if they were given isotonic saline as opposed to Ringer's lactate [31]. These effects are the consequence of acidosis mobilising potassium from the intracellular space in patients where renal function is unable to compensate for these changes. It is worth noting that there was no adverse effect of isotonic saline on renal function. There is no evidence of this effect in other studies comparing isotonic saline with balanced salt crystalloids [31].

Boldt and colleagues published a series of articles in which a totally balanced strategy (balanced crystalloid and balanced colloid) was compared with a standard treatment (isotonic saline and colloid in isotonic saline carrier) (Table 4). In one study, in patients undergoing major abdominal surgery there was no significant difference in urine output and in serum creatinine on the first postoperative day [18].

Another study in elderly patients undergoing cardiac surgery also reported no major impact on renal function [19]. For up to 60 days following surgery, there was no difference between the groups regarding plasma creatinine concentration. Levels of neutrophil gelatinase-associated lipocalin (NGAL) were also measured. There was a small increase on the first day after surgery in the isotonic saline-based group, but levels in both groups were near-normal by the second day. Overall NGAL values were extremely low (around 20 ng/ml), significantly below the threshold of 150 ng/ml that is considered an indicator of acute kidney injury.

Finally, a study investigating the effects of two colloid strategies in patients undergoing cardiopulmonary

bypass was also reported by Boldt and colleagues [20]. Albumin in saline carrier was compared with an HES-based colloid in balanced solution. There was no significant difference in serum creatinine following surgery; and although an increase in NGAL of 15 ng/ml was observed in the albumin group, values remained within the normal range.

It has been claimed that NGAL is an early biomarker of acute renal injury [32], but NGAL values can vary considerably even in the absence of adverse kidney effects. Using the same test as was used in the two previously mentioned studies, Wagener and colleagues reported rises of 165 to 1,490 ng/ml in cardiac surgery patients with and without acute kidney injury [33]. These results suggest that values reported by Boldt and colleagues are very low and, although the type of solution significantly influenced the NGAL values, there is no indication of significant impairment in renal function.

In conclusion, no significant differences in creatinine variations have been reported and only slight differences in NGAL, not clinically relevant, were observed. From these results one may conclude there is no convincing difference between isotonic saline strategies and balanced strategies in terms of renal function.

Effects of dilutional-hyperchloraemic acidosis on coagulation and bleeding

Data from *in vitro* studies suggest that balanced solutions may have fewer negative effects on coagulation parameters [34,35]. The authors acknowledge the inherent problems of *in vitro* studies, however, which include the effects of haemodilution, calcium dilution and the absence of physiological components such as the endothelium. Owing to these significant limitations, no clinically relevant conclusions can be drawn from *in vitro* studies.

Clinical studies provide more relevant insights. Boldt and colleagues compared the effects of very high doses (around 18 litres in 48 hours) of Ringer's lactate and isotonic saline in patients undergoing abdominal surgery (Table 3) [16]. There was no significant difference in coagulation tests and in blood loss between the groups.

Waters and colleagues compared Ringer's lactate with isotonic saline in patients undergoing repair of abdominal and thoracoabdominal aortic aneurysm (Table 5) [36]. There was a small but nonsignificant difference in blood loss in favour of the Ringer's lactate group (Table 5). There was no significant difference in the use of packed red blood cells or fresh-frozen plasma between the two groups. The only statistically significant difference was a higher volume of platelet transfusion in the saline group. When all blood products were summed, the use of blood products was significantly higher in the saline group. Both groups included patients with thoracoabdominal aneurysm, however, which may account for the high variability in blood loss and transfusion requirements. No significant difference in morbidity or mortality was reported.

Studies investigating the use of colloids also found no difference in blood loss between colloids in balanced solutions and those in isotonic saline solutions. Kulla and colleagues did not observe differences in blood loss patients undergoing abdominal surgery, and all other coagulation parameters were not significantly different between the two groups [21]. A similar study by Boldt and colleagues also found no difference in blood loss between the two groups (Table 5) [18].

Only one study reported differences between isotonic saline-based and balanced colloids. Comparing HES 130/0.42 in balanced solution with albumin in saline as a priming solution for cardiopulmonary bypass, Boldt and colleagues reported small but significant differences in coagulation (Rotem, Pentapharm, Munich, Germany) in favour of the balanced HES. This observation was associated with significantly lower blood loss [20]. Similarly, use of blood products throughout and after surgery was significantly lower in the HES group (Table 5). The number of patients in each group was very small (n = 25), however, given that coagulation and bleeding in cardiac surgery may be highly variable. A recent study performed by the same investigators in the same setting (cardiac surgery), comparing a balanced HES with albumin, did not confirm these results [22].

In conclusion, there is little evidence that large volumes of isotonic saline have a significantly detrimental effect on coagulation, blood loss or transfusion.

Effects of dilutional-hyperchloraemic acidosis on gastrointestinal function

Several studies have investigated the effects of dilutional-hyperchloraemic acidosis on gastrointestinal function with controversial results.

Williams and colleagues reported that healthy volunteers receiving saline experienced more frequent abdominal discomfort than those receiving Ringer's lactate [15]. Wilkes and colleagues investigated the effects of 6% hetastarch in a balanced carrier plus Ringer's lactate versus hetastarch in saline plus isotonic saline in elderly surgical patients [37]. The only difference related to gastrointestinal function was a small difference in the gastric CO_2 gradient, which showed a larger increase in the saline group. The difference is small and probably not clinically relevant (0.3 ± 1.5 kPa in the Ringer's lactate group compared with 1.0 ± 0.7 kPa in the saline group), but may suggest a better gastric mucosal perfusion in the Ringer's lactate group. A nonsignificant trend towards more nausea and vomiting was observed in the saline group.

Table 5. Blood loss in studies comparing a balanced strategy with a saline-based strategy

Study	Group	Blood loss (ml)	*P* value between groups
Crystalloids only			
Waters and colleagues [36]	Ringer's lactate	2,300 (1,600 to 3,500)	NS
	Isotonic saline	2,900 (1,930 to 4,000)	
Boldt and colleagues [16]	Ringer's lactate	1,830 ± 380	NS
	Isotonic saline	1,730 ± 390	
Colloids and crystalloids			
Kulla and colleagues [21]	HES 130/0.42 + Ringer's acetate	1,156 ± 917	NS
	HES 130/0.42 + modified saline	1,228 ± 691	
Boldt and colleagues [18]	HES 130/0.42 + modified RL	1,798 ± 1,220	NS
	HES 130/0.42 + isotonic saline	1,557 ± 1,165	
Boldt and colleagues [19]	HES 130/0.42 + modified RL	1,510 ± 410	NS
	HES 130/0.42 + isotonic saline	1,380 ± 460	
Boldt and colleagues [20]	HES 130/0.42 + modified RL	1,200 ± 290	<0.05
	Albumin 5% + isotonic saline	1,520 ± 210	
Boldt and colleagues [22]	HES 130/0.40 + modified RL	1,380 ± 460	NS
	Albumin 5% + isotonic saline	1,510 ± 410	

HES, hydroxyethyl starch; RL, Ringer's lactate.

Moretti and colleagues reported different results. Patients were randomised into three groups to compare the effects of hetastarch in isotonic saline, of hetastarch in balanced solution and of Ringer's lactate on postoperative outcomes [38]. While there was no significant difference in the incidence of nausea and use of antiemetics between the hetastarch groups, both were significantly lower than in the Ringer's lactate group (Table 6). The authors concluded that intraoperative fluid resuscitation with colloids, compared with crystalloids, improved postoperative recovery with regards to postoperative nausea and vomiting. These results suggest that fluid volume may be more important than composition. Several other studies suggest that intraoperative crystalloid restriction may be associated with an improvement in gastrointestinal function and a decrease in postoperative complications [39-41].

In conclusion, there is not sufficient evidence from the available literature to suggest that dilutional-hyperchloraemic acidosis has a clinically relevant effect on gastrointestinal function. Some degree of intraoperative crystalloid restriction and colloid use may, however, be associated with an improvement in gastrointestinal function and outcome.

Effects of dilutional-hyperchloraemic acidosis on mortality

Metabolic acidosis is often associated with adverse outcomes; however, it is important to differentiate between the effects of acidosis itself and the conditions that cause it. In the clinical setting, metabolic acidosis arises from different causes, within which hyperchloraemia may play a role. Following trauma, for example, major metabolic acidosis has been reported in relation to severe hypovolaemia, tissue hypoxia and shock. In this situation, it is very difficult to determine the specific role of isotonic saline administration and the potential impact of other mechanisms on outcome [42-45].

Experimental studies may therefore be useful to understand the impact of fluid therapy on outcome. Short-term survival was measured in a model of experimental sepsis with rats resuscitated with a balanced hetastarch, Ringer's lactate or isotonic saline [46]. In terms of mortality, Ringer's lactate was no better than isotonic saline. The best survival was observed in the colloid group, suggesting that a colloid strategy may be favourable in sepsis.

Gunnerson and colleagues carried out an observational, retrospective review of hospital data of 9,799 critically ill patients admitted to the intensive care unit [47]. They selected a cohort (n = 851) in which clinicians ordered a measurement of arterial lactate level; 584 patients (64%) had a metabolic acidosis, either related to lactate, a strong ion gap or hyperchloraemia. Mortality was highest in patients with lactate acidosis (56%). In patients with dilutional-hyperchloraemic acidosis, mortality was the same as in the control group without metabolic acidosis (Figure 4). From this observational study, it may be concluded that patients with hyperchloraemic acidosis were not associated with an increased risk of mortality compared with critically ill patients without metabolic acidosis.

Table 6. Incidence and severity of postoperative complications [38]

Variable	6% hetastarch in saline	6% hetastarch in balanced salt	Ringer's lactate	*P* value
Nausea	14 (47%)	11 (37%)	22 (73%)	0.007
Nausea severity				
1 (mild)	8	2	4	0.02
2 (moderate)	4	4	10	
3 (severe)	2	5	8	
Emesis	8 (27%)	7 (23%)	16 (53%)	0.02
Rescue antiemetic	9 (30%)	8 (27%)	18 (60%)	0.006

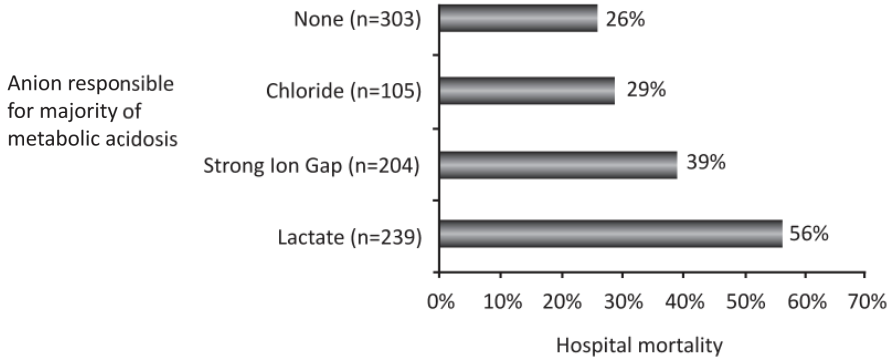

Figure 4. Hospital mortality associated with type of metabolic acidosis. Mortality associated with the major ion contributing to the metabolic acidosis. Hospital mortality associated with the various causes of metabolic acidosis (standard base excess (SBE) <–2). Mortality percentage is mortality within each subgroup, not a percentage of overall mortality. Lactate indicates that lactate contributes to at least 50% of the SBE; SIG, strong ion gap contributes to at least 50% of SBE (and not lactate); hyperchloraemic, absence of lactate or SIG acidosis and SBE <–2; none, no metabolic acidosis (SBE ≥–2 mEq/l). *P* <0.001 for the four-group comparison. Adapted from Gunnerson and colleagues [47].

Noritomi and colleagues performed an observational study in 60 patients with severe sepsis and septic shock [48]. In this group of patients, mortality was significantly associated with an increased inorganic ion difference. The difference in plasma chloride concentrations between survivors and nonsurvivors was minimal (3 mEq/l). Of note in the Rivers study, a difference in base excess of 5 mEq/l after 6 hours of treatment was observed between optimised patients and controls, with a concomitant reduced mortality in the patients receiving the highest dose of colloids and crystalloids (6 litres versus 4.5 litres) [49]. In their study, however, several confounding variables might have influenced the acid–base status and the mortality is more related to the cause of acidosis rather than to transient dilutional-hyperchloraemic acidosis.

In a prospective observational study set in the paediatric intensive care unit following cardiac surgery, Hatherill and colleagues documented that dilutional-hyperchloraemic acidosis was associated with reduced requirement for adrenaline therapy [50]. It is suggested that dilutional-hyperchloraemic acidosis is a benign phenomenon that should not prompt escalation of haemodynamic support.

In another prospective observational trial, Brill and colleagues studied 75 consecutive surgical intensive care patients with base deficits >2.0 mmol/l. Patients were divided into those with hyperchloraemic acidosis and those with acidosis from other causes. There were no significant differences in age, Acute Physiology and Chronic Health Evaluation II scores, or volumes of resuscitation between the hyperchloraemic group and the remaining patients. There were four deaths (10.8%) in the hyperchloraemic group and 13 deaths (34.2%) in the remaining patients ($P = 0.03$). The authors concluded that hyperchloraemic acidosis is a common cause of base deficit in the surgical intensive care unit, associated with lower mortality than base deficit secondary to another cause [51]. Maciel and Park have reported similar results [52].

Conclusion

The current review has presented an extensive analysis of all available studies using balanced solutions. We conclude that dilutional-hyperchloraemic acidosis is a side effect, mainly observed after the administration of large volumes of isotonic saline as a crystalloid. In this particular setting, however, the effect remains moderate

and relatively transient (24 to 48 hours), and is minimised with the use of olloids, whatever the nature of the carrier. From the available literature, the evidence for adverse effects of dilutional-hyperchloraemic acidosis on organ function, morbidity or mortality remains of small importance. In addition, the use of colloids together with crystalloids allows a reduction of the total volume of fluids used and considerably limits the chloride load.

In view of the substantial experimental and clinical information on the efficacy and safety of various colloids, including third-generation HES (HES 130/0.4), and of the limited published information on the effects of balanced solutions on outcome, we cannot changing to a new generation of colloids until there is evidence suggesting genuine detriment from existing fluids and clear evidence of benefit with new solutions.

Key messages

- The term dilutional-hyperchloraemic accurately defines a decrease in base excess, or a decrease in SID, associated with hyperchloraemia and a normal anion gap.
- Isotonic saline describes the main property of 0.9% saline solution. It is neither normal, abnormal nor unbalanced. Balanced solutions is a general term to describe different solutions with different electrolyte compositions.
- Dilutional-hyperchloraemic acidosis is a moderate and relatively transient side effect, minimised or avoided by limiting crystalloid administration through the use of colloids in any carrier.
- No convincing evidence for clinically relevant adverse effects of dilutional-hyperchloraemic acidosis on morbidity or mortality can be found.
- Following extensive review, owing to the limited published information on the effects of balanced solutions on outcome, the change of practice from colloids in isotonic saline to balanced colloid use cannot be recommended.

Abbreviations

A_{tot}, sum of all anionic charges of weak plasma acids; CO_2, carbon dioxide; HES, hydroxyethyl starch; NGAL, neutrophil gelatinase-associated lipocalin; PCO_2, partial pressure of carbon dioxide; SID, strong ion difference.

Competing interests

BG has received honoraria and financial reimbursements from Fresenius Kabi for lecturing and authorship, and from Laboratoire Français du Fractionnement et des Biotechnologies for lecturing; he is the principal clinical trial investigator in the Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients With Severe Sepsis (CRYSTMAS Trial), sponsored by Fresenius Kabi. NS has received honoraria and financial reimbursements from Fresenius Kabi; his nonfinancial competing interest pertains to adverse comments made about a set of guidelines relating to fluids, both in lectures and in text. GDR has received honoraria for attending a Fresenius Kabi advisory board meeting. SK has received honoraria for lecturing, and reimbursements for travel and hotel accommodation from Fresenius Kabi and B Braun. BV has received consulting fees and honoraria from B Braun, Baxter and Fresenius Kabi. DA has received honoraria for attending a Fresenius Kabi advisory board meeting. MJ has received honoraria for lectures from several fluid companies, particularly Fresenius Kabi; he was given an unrestricted educational grant from Fresenius Kabi for the First Randomised Controlled, Double-blind Study of Crystalloids vs Colloids in Trauma (FIRST Trial).

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References

1. Powell-Tuck J, Gosling P, Lobo DN, Allison SP, Carlson GL, Gore M, Lewington AJ, Pearse RM, Mythen MG: *British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP).* London: NHS National Library of Health; 2009.
2. Liu B, Finfer S: **Intravenous fluids in adults undergoing surgery [editorial].** *Br Med J* 2009, **339:**3-4.
3. Handy JM, Soni N: **Physiological effects of hyperchloraemia and acidosis.** *Br J Anaesth* 2008, **101:**141-150.
4. Shaneyfelt TM, Centor RM: **Reassessment of clinical practice guidelines: go gently into that good night.** *JAMA* 2009, **301:**868-869.
5. Hasselbalch KA: **Die berechnung der wasserstoffzahl des blutes auf der freien und gebundenen kohlensaure desselben, und die sauerstoffbindung des blutes als funktion der wasserstoffzahl.** *Biochem Z* 1916, **78:**112-144.
6. Stewart PA: **Modern quantitative acid–base chemistry.** *Can J Physiol Pharmacol* 1983, **61:**1444-1461.
7. Yunos NM, Bellomo R, Story D, Kellum J: **Bench-to-bedside review: chloride in critical illness.** *Crit Care* 2010, **14:**226.
8. Constable PD: **Hyperchloremic acidosis: the classic example of strong ion acidosis.** *Anesth Analg* 2003, **96:**919-922.
9. Morgan TJ, Venkatesh B: **Designing 'balanced' crystalloids.** *Crit Care Resusc* 2003, **5:**284-291.
10. Doberer D, Funk G-C, Kirchner K, Schneeweiss B: **A critique of Stewart's approach: the chemical mechanism of dilutional acidosis.** *Intensive Care Med* 2009, **35:**2173-2180.
11. Kurtz I, Kraut J, Ornekian V, Nguyen MK: **Acid–base analysis: a critique of the Stewart and bicarbonate-centered approaches.** *Am J Physiol Renal Physiol* 2008, **294:**F1009-F1031.
12. Lang W, Zander R: **Prediction of dilutional acidosis based on the revised classical dilution concept for bicarbonate.** *J Apply Physiol* 2005, **98:**62-71.
13. Rehm M, Finsterer U: **Treating intraoperative hyperchloremic acidosis with sodium bicarbonate or tris-hydroxymethyl aminomethane: a randomized prospective study.** *Anesth Analg* 2003, **96:**1201-1208.
14. Scheingraber S, Rehm M, Sehmisch C, Finsterer U: **Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynaecologic surgery.** *Anesthesiol* 1999, **90:**1265-1270.
15. Williams EL, Hildebrand KL, McCormick SA, Bedel MJ: **The effect of intravenous lactated Ringer's solution versus 0.9% sodium chloride solution on serum osmolality in human volunteers.** *Anesth Analg* 1999,

88:999-1003.
16. Boldt J, Haisch G, Suttner S, Kumle B, Schellhase F: **Are lactated Ringer's solution and normal saline solution equal with regard to coagulation?** *Anesth Analg* 2002, **94:**378-384.
17. Base E, Standl T, Mahl C, Jungheinrich C: **Comparison of 6% HES 130/0.4 in a balanced electrolyte solution versus 6% HES 130/0.4 in saline solution in cardiac surgery [abstract].** *Crit Care* 2006, **10:**176.
18. Boldt J, Schöllhorn T, Münchbach J, Pabsdorf M: **A total balanced volume replacement strategy using a new balanced hydroxyethyl starch preparation (6% HES 130/0.42) in patients undergoing major abdominal surgery.** *Eur J Anaesthesiol* 2007, **24:**267-275.
19. Boldt J, Suttner S, Brosch C, Lehmann A, Roehm K, Mengistu A: **The influence of a balanced volume replacement concept on inflammation, endothelial activation, and kidney integrity in elderly cardiac surgery patients.** *Intensive Care Med* 2009, **35:**462-470.
20. Boldt J, Suttner S, Brosch C, Lehmann A, Roehm K, Mengistu A: **Cardiopulmonary bypass priming using a high dose of a balanced hydroxyethyl starch versus an albumin-based priming strategy.** *Anesth Analg* 2009, **109:**1752-1762.
21. Kulla M, Weidhase R, Lampl L: **Hydroxyethyl starch 6% 130/0.42 in acetate-buffered Ringer's solution as a part of a balanced-volume resuscitation in abdominal surgery.** *Anasth Intensivmed* 2008, **49:**7-18.
22. Boldt J, Mayer J, Brosch C, Lehmann A, Mengistu A: **Volume replacement with a balanced hydroxyethyl starch (HES) preparation in cardiac surgery patients.** *J Cardiothorac Vasc Anesth* 2010, **24:**399-407.
23. O'Dell E, Tibby SM, Durward A, Murdoch IA: **Hyperchloremia is the dominant cause of metabolic acidosis in the postresuscitation phase of pediatric meningococcal sepsis.** *Crit Care Med* 2007, **35:**2390-2394.
24. Boldt J, Ducke M, Kumle B, Papsdorf M, Surmeyer EL: **Influence of different volume replacement strategies on inflammation and endothelial activation in the elderly undergoing major abdominal surgery.** *Intensive Care Med* 2004, **30:**416-422.
25. Kotchen TA, Luke RG, Ott CE, Galla JH, Whitescarver W: **Effect of chloride on renin and blood pressure responses to sodium chloride.** *Ann Intern Med* 1983, **98:**817-822.
26. Wilcox CS: **Regulation of renal blood flow by plasma chloride.** *J Clin Invest* 1983, **71:**726-735.
27. Wilcox CS, Peart WS: **Release of renin and angiotensin II into plasma and lymph during hyperchloremia.** *Am J Physiol* 1987, **4:**734-741.
28. Quilley CP, Lin Y-S, McGiff JC: **Chloride anion concentration as a determinant of renal vascular responsiveness to vasoconstrictor agents.** *Br J Pharmacol* 1993, **108:**106-110.
29. Hansen PB, Jensen BL, Skott O: **Chloride regulates afferent arteriolar contraction in response to depolarization.** *Hypertension* 1998, **32:**1066-1070.
30. Reid F, Lobo DN, Williams RN, Rowlands BJ, Allison SP: **(Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study.** *Clin Sci* 2003, **104:**17-24.
31. O'Malley CM, Frumento RJ, Hardy MA, Benvenisty AI, Brentjens TE, Mercer JS, Bennett-Guerrero, E: **A randomized, double-blind comparison of lactated Ringer's solution and 0.9% NaCl during renal transplantation.** *Anesth Analg* 2005, **100:**1518-1524.
32. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, Syed, Ali S, Barasch J, Devarajan P: **Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study.** *Clin J Am Soc Nephrol* 2008, **3:**665-673.
33. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT: **Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery.** *Am J Kidney Dis* 2008, **52:**425-433.
34. Boldt J, Wolf M, Mengistu A: **A new plasma-adapted hydroxyethylstarch preparation: in vitro coagulation studies using thrombelastography and whole blood aggregometry.** *Anesth Analg* 2007, **104:**425-430.
35. Boldt J, Mengistu A, Seyfert U, Vogt A, Hellstern P: **The impact of a medium molecular weight, low molar substitution hydroxyethyl starch dissolved in a physiologically balanced electrolyte solution on blood coagulation and platelet function in vitro.** *Vox Sang* 2007, **93:**139-144.
36. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR: **Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study.** *Anesth Analg 2001*, **93:**817-822.
37. Wilkes NJ, Woolf R, Mutch M, Mallett SV, Peachey T, Stephens R, Mythen MG: **The effects of balanced versus saline-based hetastarch and crystalloid solutions on acid–base and electrolyte status and gastric mucosal perfusion in elderly surgical patients.** *Anesth Analg* 2001, **93:**811-816.
38. Moretti EW, Robertson KM, el-Moalem H, Gan TJ: **Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration.** *Anesth Analg* 2003, **96:**611-617.
39. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP: **Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial.** *Lancet* 2002, **359:**1812-1818.
40. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einay S, Matot I: **Effect of intraoperative fluid management on outcome after intra-abdominal surgery.** *Anesthesiology* 2005, **103:**25-32.
41. Brandstrup B, Tonnesen E, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, Rasmussen MS, Lanng C, Wallin L, Iversen LH, Gramkow CS, Okholm M, Blemmer T, Svendsen PE, Rottensten HH, Thage B, Rils J, Jeppesen IS, Teilum D, Christensen AM, Graungaard B, Pott F: **Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial.** *Ann Surg* 2003, **238:**641-648.
42. Siegel JH, Rivkind AI, Dalal S, Goodarzi S: **Early physiologic predictors of injury severity and death in blunt multiple trauma.** *Arch Surg* 1990, **125:**498-508.
43. Rixen D, Raum M, Bouillon B, Lefering R, Neugebauer E: **Base deficit development and its prognostic significance in posttrauma critical illness: an analysis by the trauma registry of the Deutsche Gesellschaft fur Unfallchirurgie.** *Shock* 2001, **15:**83-89.
44. Rutherford EJ, Morris JA, Reed GW, Hall KS: **Base deficit stratifies mortality and determines therapy.** *J Trauma* 1992, **33:**417-423.
45. Davis JW, Parks SN, Kaups KL, Gladen HE, O'Donnel-Nicol S: **Admission base deficit predicts transfusion requirements and risk of complications.** *J Trauma* 1996, **41:**769-774.
46. Kellum JA: **Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved short-term survival and acid–base balance with Hextend compared with saline.** *Crit Care Med* 2002, **30:**300-305.
47. Gunnerson KJ, Saul M, He S, Kellum JA: **Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients.** *Crit Care* 2006, **10:**R22.
48. Noritomi DT, Soriano FG, Kellum JA, Cappi SB, Biselli PJC, Liborio AB, Park M: **Metabolic acidosis in patients with severe sepsis and septic shock: a longitudinal quantitative study.** *Crit Care Med* 2009, **37:**1-7.
49. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M: **Early goal-directed therapy in the treatment of severe sepsis and septic shock.** *N Engl J Med* 2001, **345:**1368-1377.
50. Hatherill M, Salie S, Waggie Z, Lawrenson J, Hewitson J, Reynolds L, Argent A. **Hyperchloraemic metabolic acidosis following open cardiac surgery.** *Arch Dis Child* 2005, **90:**1288-1292.
51. Brill SA, Stewart TW, Brundage SI, Schreiber MA. **Base deficit does not predict mortality when secondary to hyperchloremic acidosis.** *Shock* 2002, **17:**459-462.
52. Maciel AT, Park M: **Differences in acid–base behavior between intensive care unit survivors and nonsurvivors using both a physicochemical and a standard base excess approach: a prospective, observational study.** *J Crit Care* 2009, **24:**477-483.

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Fluid Resuscitation for Trauma Patients: Crystalloids Versus Colloids

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Abstract Controversy regarding the role of colloids in the resuscitation of trauma patients has persisted for the past century without a clear resolution. Recently, the early treatment goals of traumatic hypovolemic shock have changed with an emphasis on minimal intravenous fluid administration and the avoidance of over-resuscitation. While some clinicians see a role for colloids in this model, others have become wary as evidence mounts against the efficacy and safety of hydroxyethyl starch and human albumin in critically ill patients. We reviewed the history and fundamentals of the crystalloid versus colloid debate and explored the relevant findings from the prominent non-trauma literature with attention to their applicability in the trauma population. Critical appraisal of the trauma-specific colloid literature is offered with a focus on study design and practical utility. Finally, we offer recommendations about the rational selection of fluids for clinicians who treat these challenging patients.

Keywords Trauma · Crystalloid · Colloid · Resuscitation · Fluid therapy · Plasma substitutes

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Introduction

Traumatic injury is a frequent occurrence throughout the world, the third leading overall cause of death in the USA, and the main cause of death in people between ages 1 and 44 [1]. Out of fatalities resulting from trauma, hemorrhage has been suggested as the second most common contributing cause of death, with the majority of mortality occurring within 48 h of the inciting injury [2, 3]. Similarly, hemorrhage was the cause of intraoperative death in 82 % of patients following major trauma in one series [4]. Intravenous crystalloid and colloid solutions play a critical role in pre-hospital care, initial resuscitation, and as an adjunct to transfusion during ongoing resuscitative efforts. While there is considerable worldwide variability in preference for resuscitation with either crystalloid or colloid, and for the types of colloids preferred, the utility of albumin and hydroxyethyl starch (HES) in trauma patients will be reviewed herein [5].

Background

The Science of Intravenous Fluids: A Brief Summary

The Starling equation, which links net fluid movement between compartments with capillary versus interstitial hydrostatic and oncotic pressure, has traditionally been used by proponents of colloid resuscitation to describe fluid dynamics in vivo. The terms crystalloid and colloid trace their origin back to Thomas Graham, who in 1861 described aqueous solutions with the ability to readily diffuse through membranes as crystalloids, versus colloids that did not [6]. While time has shown this definition to be somewhat flawed, the monikers have remained. Crystalloids

consist of mineral salts in aqueous solution with or without other water-soluble molecules, such as buffers. Following administration, the volume of infusate quickly equilibrates across the entire extracellular fluid (ECF) volume, for which the interstitial compartment accounts for 75 %, versus only 25 % for the intravascular compartment. [Note that the terms first, second, and third space refer to the intravascular, extravascular (interstitial plus intracellular), and nonfunctional compartments, respectively]. Colloids contain solutes large enough to exert an oncotic pressure and should confer a hypothetical benefit of prolonged intravascular permanence compared to crystalloids, which forms the foundation of the debate at hand.

Attention has been drawn recently to the role of the endothelial glycocalyx, which forms a carbohydrate-rich barrier along the apical surface of vascular endothelial cells. The glycocalyx itself exerts an oncotic force such that the classic Starling model has required revision [7, 8]. As our understanding of this complex barrier continues to evolve, it has been hypothesized that its integrity can be degraded by inflammatory mediators (following ischemia or during sepsis) or mechanical stress (such as hypervolemia), at which point colloids may not be retained as completely in the intravascular compartment leading to capillary leak and potentially exacerbating tissue edema and fluid accumulation [9, 10]. As proteins are bound within and on the surface of its thick matrix, this may create an endovascular "sealing" effect. It has also been proposed that colloids interact with the glycocalyx in a complicated fashion as evidenced partly by improved coronary blood flow secondary to vasodilatation in a guinea pig heart model following albumin but not HES exposure [11]. While "glycocalyx" has become a buzzword of late and a target of translational research, clinical applications remain sparse at this time [12]. Regardless, the interaction of colloids with the vascular endothelium is not as simple as was once conceived.

Trends in Resuscitation

Based on the classic model of shock developed in the 1940s by physiologist Carl Wiggers involving induced hypovolemia in anesthetized animals, Tom Shires later demonstrated that crystalloids (in addition to blood transfusion) were necessary to replete ECF losses following prolonged hypotension secondary to controlled hemorrhage [13, 14]. This concept was adapted for use in military and civilian trauma care, and the timely administration of appreciable crystalloid volumes became standard practice. Subsequent animal models and clinical experience began to suggest that, in cases of uncontrolled hemorrhage, overzealous crystalloid resuscitation disrupted coagulation, worsened bleeding, and contributed to mortality [15]. In a landmark study published in 1994, patients with penetrating trauma for whom resuscitation was delayed until the time operative intervention were more likely to survive [16]. While the concept of delayed resuscitation is now better characterized as hypotensive or damage control resuscitation, a tenuous body of evidence hints that, in penetrating trauma, extensive resuscitation before surgical control of hemorrhage could be counterproductive [17, 18]. Accordingly, some have envisioned a role for colloids in this setting to limit the total volume of fluid administered prior to hemostasis, which is an old concept with renewed attention [19•].

Historical Perspectives on the Debate and Colloid Development

The first colloid to see significant use in humans followed the research of James Hogan in 1915, who sterilized and diluted warmed bovine gelatin in saline [20]. Hogan was quick to publicly espouse the merits of colloidal resuscitation and traveled extensively throughout the European theater during the First World War to demonstrate the preparation and application of his novel treatment [21]. Concurrently, the English physiologist Bayliss had conducted a series of experiments in animal models of "wound shock," which he remedied by sparingly administering a solution of gum arabic, a derivative of *Acacia senegalis* tree sap, in saline to supplement intravascular oncotic pressure [22]. A related solution was implemented at forward camps during the final months of World War I, thus marking the first widespread use of resuscitation with colloids [23]. Ultimately, the adoption of gelatin was delayed owing to issues with preparation and storage, and gum arabic was abandoned secondary to its hepatotoxicity and antigenicity [24, 25]. The first commercially produced synthetic colloidal resuscitation solution polyvinylpyrrolidon was synthesized by the prolific German chemist Walter Reppe in 1939 and later marketed by Bayer under the trade name Periston [26]. Periston was acquired and investigated by US researchers, who recommended against its use owing to tissue accumulation and a short intravascular half-life [27].

Alfred Blalock's work in the 1930s shifted the focus away from Bayliss' conservative and colloid-centric resuscitation practices to the critical role of whole blood (and plasma) in the treatment of hypovolemic shock to support oxygen-carrying capacity [28]. Related efforts toward the fractionation of whole blood, and subsequently plasma, led to the availability of albumin via the Cohn process [29]. While the utility of plasma as a "volume expander" was already well-established, concerns over frequent contamination with hepatitis despite desiccation to facilitate storage, and the clinical utility derived from other fractionation products (such as gamma globulin), made

albumin, which could be heat sterilized and easily stored, an attractive battlefield alternative during World War II despite increased production cost [30]. Following the aforementioned shortcomings with the synthetic colloids available, attention was drawn at the conclusion of the Second World War to dextran, a complex polysaccharide that was originally developed in Sweden while searching for a safe plasma substitute [31]. Implementation of a plasma production and stockpiling program during the Korean War suffered setbacks due to viral contamination and logistic hurtles. Accordingly, albumin and dextran were used almost exclusively at forward resuscitation facilities during the latter stages of the conflict despite the contemporary recognition that dextran prolonged bleeding time and impaired renal function [32–34].

As alluded to previously, the use of significant quantities of crystalloid for resuscitation after battlefield trauma was not commonplace until the 1960s following research associating the repletion of ECF in shock via isotonic crystalloids with improved survival [14]. This shift in practice (coupled with more aggressive blood product transfusion) reduced the incidence of renal failure and mortality during the Vietnam War; however, a new clinical entity termed "shock lung" was identified following prolonged resuscitation [35]. This came to be known as acute respiratory distress syndrome (ARDS) by the 1970s, and concern grew that iatrogenic crystalloid administration played a role in its etiology. Multiple trials were conducted in the 1980s and 1990s comparing the pulmonary effects of resuscitation with crystalloids versus colloids; however, varied populations, problematic study design and endpoints, and heterogeneous interventions made it difficult to draw conclusions. Large meta-analyses would later demonstrate no difference in the incidence of adverse pulmonary outcomes [36, 37]. However, the majority of trials were conducted in an intensive care unit (ICU) setting, leaving practitioners to wonder about the applicability of this research to trauma patients.

After nearly a century of debate, we are still faced with many of the same quandaries involving the same fluids. Questions linger as to their cost effectiveness, impact on coagulation, association with renal failure, and overall safety. Perhaps most importantly, to what degree can the large body of research from ICU, surgical, and septic patients be accurately extrapolated to the trauma population?

Colloid Use in Modern Critical Care: Implications for Trauma Patients

Hydroxyethyl Starch: From Boom to Bust

HES is derived from nonionic amylopectin sourced from either waxy maize or potato, which, when coupled with a crystalloid medium, has enjoyed great popularity over the past 20 years as a volume expander. HES products are described by their percentage in solution, average molecular weight, and number of hydroxyethyl group per glucose molecule (e.g., degree of molar substitution). Formulations with larger molecular weight and degrees of substitution persist longer intravascularly and were the initial targets of pharmaceutical development (Table 1). Hespan (6 % HES 600/0.75 in 0.9 % saline) and Hextend (6 % HES 670/0.75 in lactated electrolytes) were the first products approved by the United States Food and Drug Administration (FDA) in 1972 and 1999, respectively. However, first (heta- and hexa-starch) and second (pentastarch) generation HES products were associated with coagulopathy, prolonged storage within the reticulo-endothelial system, and long-term renal impairment [38–41]. Accordingly, efforts were then directed toward the creation of a "third generation" product, which resulted in two tetrastarch formulations: Voluven (6 % HES 130/0.4 in 0.9 % saline) and Tetraspan (6 % HES 130/0.42 in Ringer's lactate). After their release, a commercial marketing push was followed by papers espousing a similar efficacy profile to prior HES generations with a reduced likelihood of adverse effects [42–44]. Joachim Boldt, a German anesthesiologist with a long track record of prolific HES research and industry ties, was quick to espouse the benefits of these new products. Boldt later came under scrutiny for failure to secure institutional review board approval for multiple studies, and evidence suggesting widespread data falsification has ultimately led to the retraction of approximately 90 publications [45]. In addition to casting doubt on meta-analyses containing the implicated results, these developments have also served to paint HES in a negative light overall [46••, 47].

These setbacks were followed by the publication of the Scandinavian Starch for Severe Sepsis/Shock (6S) trial, the Crystalloid versus HES Trial (CHEST), and the Crystalloids Morbidity Associated with Severe Sepsis (CRYSTMAS) trial, all of which linked tetrastarch with adverse outcomes [48•, 49•, 50]. When coupled with the Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study, which examined the effects of pentastarch, these four large randomized control trials (RCTs) served to cast further doubt on the efficacy and safety of HES [51]. Discussion of their relative merits and weakness lies beyond the scope of this review and has been the subject of much debate [52, 53]. In summary, these pivotal studies suggest that HES is deleterious in septic or otherwise critically ill patients with an associated increased risk of mortality and renal failure (Table 2). Following a similar move by their European counterpart, the FDA added a boxed warning to all HES products that advises health professionals against their use in patients with critical illness, sepsis, pre-existing renal dysfunction, and severe liver disease [54].

Table 1 FDA-Approved hydroxyethyl starch (HES) products

Trade name	Manufacturer	HES %	Mean molecular weight (kD)	Molar substitution	Diluent	Year licensed by FDA	Available as generic (Y/N)
Hespan	B. Braun	6	670	0.75	0.9 % sodium chloride	1972	Y (Teva)
Hextend	BioTime	6	600	0.75	Lactated electrolyte solution	1999	N
Voluven	Fresenius Kabi	6	130	0.4	0.9 % sodium chloride	2007	N

FDA United States Food and Drug Administration, *kD* kilodaltons

Replacement Ratios: Sparse Volume-Sparing

Traditional teaching holds that crystalloids must be administered in a 3:1 ratio to achieve similar intravascular volume expansion as that of whole blood or colloids. This dictum stems largely from old and limited experimental animal models but nevertheless has been long-perpetuated [14, 55, 56]. Accordingly, one point often argued in favor of colloids is that their greater oncotic pressure and prolonged intravascular presence should result in a "volume-sparing" effect. However, in clinical practice, the ratio of crystalloid to colloid needed to achieve similar hemodynamic parameters appears to be smaller. In the VISEP, 6S, CHEST, CRYSTMAS, and CRISTAL trials, patients received, respectively, an approximate 1.4:1, 1.1:1 (non-significant), 1.15:1, 1.2:1, and 1.5:1 ratio of crystalloid to colloid to obtain similar resuscitative endpoints in ICU patients [48–51, 57]. In the Saline Versus Albumin Fluid Evaluation (SAFE) and Albumin Italian Outcome Sepsis (ALBIOS) trials, the ratios of crystalloid to albumin required for resuscitation were 1.4:1 and 1:1 [58, 59•]. Accordingly, colloids appear to confer, at best, a small benefit when examining total fluid administration.

Transfusion Requirements and Coagulopathy: A Consistent Trend

As mentioned previously, multiple studies have linked the administration of HES to both coagulopathy and increased transfusion requirements in cardiothoracic, general surgical, and septic patients [60–63]. These clinical findings have been paired with in vivo and in vitro investigations as to the effect of HES on coagulation as measured by thromboelastography, which were recently reviewed [64]. In summary, the authors analyzed 24 studies, 19 of which demonstrated coagulopathy following the administration of hetastarch. While clotting time was not consistently prolonged, weaker clot formation by virtue of impaired platelet aggregation, and fibrin cross-linking was demonstrated in patients who received tetrastarch compared to crystalloids or albumin.

Current Evidence on Colloid Use in Trauma

Albumin and the SAFE Trial

Albumin has been used widely for resuscitation since its development in the 1940s despite, what might now be considered as, limited clinical investigation before its implementation. In 1998, a Cochrane review linking albumin use in critically ill patients with increased mortality drew incredible attention from the medical community and mainstream press to what was, at the time, a $1.5 billion USD worldwide industry [65, 66]. Sales of albumin subsequently faltered until later meta-analyses emerged that painted albumin in a somewhat more favorable light [36, 67–69]. The SAFE Study aimed to resolve questions from these conflicting analyses [58]. The investigators hypothesized that administration of 4 % albumin or 0.9 % sodium chloride for resuscitation in a multi-center heterogeneous ICU setting would not have an impact on 28-day all cause mortality.

After randomizing nearly 7,000 patients, no significant difference was detected in 28 day mortality, length of ICU admission, or survival times. When comparing albumin and saline within all 1,186 patients with trauma, the relative risk of death in the albumin group was 1.36 but with a confidence interval just crossing unity (0.99–1.86, $P = 0.06$). Of note, subgroup analysis of trauma patients who had received albumin revealed an increased relative risk of death at 28 days attributed to the 7 % of the study population traumatic brain injury (TBI). A subsequent post hoc follow-up study (SAFE-TBI) also found significantly increased mortality at 24 months [70]. Compared to patients with GCS scores of 9-15, those with scores of 3-8 had significantly worse outcomes. Although, as the authors themselves mention, the relatively small sample size does not support a definitive conclusion, these findings underscore the potential for harm in patients with severe TBI. One theory is that albumin may lead to increased intracranial pressure, reduced cerebral profusion pressure, and thus poor outcomes as examined in a second post hoc analysis (SAFE-TBI II) [71].

Table 2 Landmark hydroxyethyl starch (HES) trials

Study (Authors)	Study fluid	Control fluid	*N*	Study population	Primary endpoint	Findings
VISEP (Brunkhorst et al. [51])	HES 200/0.5	Ringer's lactate	537	Severe sepsis	28 day mortality	Higher incidence of renal failure, thrombocytopenia, and transfusion with HES
CRYSTMAS (Guidet et al. [50])	HES 130/0.4	0.9 % Sodium Chloride	196	Severe Sepsis	Volume required for resuscitation	No difference in renal failure or mortality
6S (Perner et al. [48])	HES 130/0.42	Ringer's acetate	798	Severe sepsis	90 day mortality, need for RRT	Increased morality, need for RRT, and transfusion with HES
CHEST (Myburgh et al. [49])	HES 130/0.4	0.9 % Sodium Chloride	6742	Heterogeneous ICU	90 day mortality	Increased incidence of renal injury, need for RRT, and transfusion with HES
CRISTAL (Annane et al. [57])	Varied	Varied	2,857	Heterogeneous ICU	28 day mortality	No difference in 28 day mortality following varied colloids

VISEP efficacy of volume substitution and insulin therapy in severe sepsis, *CRYSTMAS* crystalloids morbidity associated with severe sepsis, *6S* Scandinavian starch for severe sepsis/septic shock, *RRT* renal replacement therapy, *CHEST* crystalloid versus hydroxyethyl starch trial, *ICU* intensive care unit, *CRISTAL* colloids versus crystalloids for the resuscitation of the critically ill

First and Second Generation HES: Military and Civilian Experiences

As reviewed previously, the military has long employed colloids for resuscitation. Starting in 1996, immediate infusion of one liter of Hespan was advocated for Special Forces medics treating those with shock in the setting of controlled hemorrhage [72]. Subsequent evaluation beginning in 1998 drew attention to HES as an option for initial casualty resuscitation beyond just the special forces arena, and in 2002 the widely employed Tactical Combat Casualty Care (TCCC) guidelines were amended to recommend up to one liter of Hextend [73–76]. Treatment with a volume greater than one liter was not recommended over concerns for coagulopathy and as failure to respond likely suggests poor hemostasis. In addition to heat tolerance, robust packaging, and cost savings over albumin, HES also has an appreciable weight advantage over crystalloids when faced with delayed patient transport owing to its prolonged duration of action, which is a major logistical advantage [76, 77]. Interestingly, up to one half of military pre-hospital providers continue to use crystalloid solutions despite the TCCC recommendations [78].

The first study to examine the efficacy and safety of HES in a civilian setting was conducted in 2008 at Ryder Trauma Center in Miami, Florida [79]. During initial resuscitation, all trauma patients without burns were eligible to receive 500–1,000 ml of open-label Hextend immediately upon arrival at the discretion of the admitting surgeon in addition to SOC with crystalloids and blood products. Ultimately, 1,714 patients with blunt or penetrating trauma were enrolled, 805 received HES, and 909 did not. Univariate analysis showed overall mortality in HES patients to be lower; however, multivariate analysis with logistic regression accounting for other baseline measures and influences on mortality did not demonstrate a significant difference. Patients with penetrating compared to blunt trauma who received HES were found to have lower overall morality (4.4 vs. 13 %, $P = 0.0016$). However, HES administration was associated with significantly higher rates of ICU admission, blood product transfusion, sepsis, and ARDS. A retrospective review by the same authors found that, in 281 patients requiring emergency surgery after admission for trauma, use of Hextend was associated with anemia, thrombocytopenia, increased likelihood of transfusion, and no difference in mortality [80].

The only other large study to have investigated the effects of resuscitation with hetastarch in trauma came from Shock Trauma at the University of Maryland Medical Center [81•]. In a retrospective fashion, trauma patients admitted to an ICU, with an injury severity score of 9 or greater, and who survived longer than 24 h were identified. Of those, 491 patients received Hespan. The mean dose of

HES was 725 ± 400 ml, and blunt trauma accounted for 85 % of all patients. Overall unadjusted in-hospital mortality was higher among patients who received HES and remained significant after adjustment for other variables (1.96, 95 % CI 1.49–2.58, $P < 0.0001$). Sub-group analysis of patients who received HES and did not undergo surgery again demonstrated increased mortality (OR 2.81, 95 % CI 1.89–4.18, $P < 0.001$). Total fluid administration, blood product utilization, and the incidence of acute kidney injury were significantly higher in the HES group. Finally, among patients with TBI, use of HES was associated with increased mortality (OR 2.51, 95 % CI 1.77–3.54).

Both studies have limitations that preclude any definitive statements based on their findings. The Ryder study was neither randomized nor blinded owing to state law that does not allow for community consent. The unavoidable mortality associated with catastrophic traumatic injury and the practical difficulties of retrieving and administering study fluid during that hectic time further increase the likelihood of selection bias. While the authors posit that survival bias may explain the worsened outcomes in patients who received HES, ultimately the study is unable to definitively establish either a safety or efficacy profile for HES in trauma patients. Like any retrospective database review, the Shock Trauma study also has multiple inherent limitations. The authors did not distinguish between blunt and penetrating trauma in their statistical analysis and, given that 85 % of patients who received HES sustained blunt trauma, their findings may be driven by that population. As in the Miami study, they identified an association between HES and increased transfusion requirements. Considering the above finding, use of HES in patients with blunt trauma (possibly including TBI) does not appear to confer a benefit and may be deleterious in several regards.

Although pentastarch formulations are not currently approved by the FDA, two small studies are mentioned herein for the sake of completeness. Examining a total of 64 patients, the effects of HES 10 % 250/0.45 versus crystalloid infusion in the early resuscitation of trauma patients were investigated, and neither study demonstrated a mortality difference [82, 83]. Small study size, use of a hyperoncotic HES preparation, and lack of FDA approval for these solutions severely limit the impact and applicability of these findings to current clinical practice.

Tetrastarch and the Fluids in Resuscitation of Severe Trauma (FIRST) Trial

To date, the FIRST trial is the only published randomized controlled trial to examine the effects of HES in blunt or penetrating trauma patients [84•]. At a single center in Cape Town, South Africa, blunt and penetrating trauma patients who had received a maximum of 2 liters of crystalloid were randomized to receive either HES 130/0.4 (Voluven) or normal saline for further resuscitation. Over the course of three years, 115 of 140 eligible patients were enrolled, and 109 were ultimately analyzed. Of those, 42 patients suffered blunt trauma and 67 had penetrating trauma. No difference in mortality was seen. Patients with penetrating trauma randomized to saline received significantly more fluid within the first 24 h and had a higher incidence of renal failure (16 vs. 0 %, $P = 0.018$). Per subsequent published communication from the authors, patients with penetrating trauma who received HES demonstrated significantly lower lactate levels versus those who received saline with an average difference of 0.68 (95 % CI 0.07–1.29, $P = 0.029$) when accounting for the marked differences in baseline lactate levels [85]. Blunt trauma patients who received HES required significantly more blood products within the first 24 h.

It is inadvisable to draw concrete conclusions from the data presented above for several reasons. The study was manufacturer-sponsored and initially designed to primarily address the volume of fluid required for resuscitation and time until return of bowel function with no intent to examine mortality, renal failure, or coagulopathy [86]. While the authors were quick to tout the improvement in lactate clearance and markers of reunal function, most adverse outcomes listed above were downplayed. In addition to the possibility of funding and reporting bias, the study was also likely underpowered to detect renal failure given the small sample size. Marked baseline differences in the blunt trauma arm of the study preclude any determination about the utility or safety of HES in that subset, and findings based on analysis non-randomized subgroups may be skewed. A similar manufacturer-sponsored trial was conducted in 2009; however, results have yet to be published [87].

Conclusion

Despite the theoretical benefits to resuscitation with colloids, the clinical evidence available does not support their role for resuscitation in trauma or otherwise critically ill patients. We agree with the authors of the recent Cochrane Review that examined the role of colloids for resuscitation in trauma, burn, and surgical patients, which concluded that "as colloids are not associated with an improvement in survival and are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified" [46••]. As reviewed above, the non-trauma literature suggests that neither HES nor albumin confers a meaningful volume-sparing effect. The trend toward increased transfusion requirements likely secondary to coagulopathy is evident in both sets of the literature. Furthermore, the use of even modern HES formulations has been associated with increased mortality and renal failure.

The initial evidence for the utility and safety of HES following trauma-induced hypovolemic shock was confined to a body of animal studies with varying quality, a review of which is beyond the scope of this discussion. Clinical management based on animal models of colloid resuscitation in shock has led to ultimately false conclusions and deleterious patient outcomes at several points in the history of this debate as summarized previously. Admittedly, there are practical barriers to RCTs in this population: consent, the impact of overwhelming injuries on unavoidable early mortality with subsequent failure of randomization, the conduct of a trial during frenzied resuscitation, and a highly variable patient population. At present, we are faced with a paucity of high-quality clinical studies addressing outcomes of colloid resuscitation in trauma. Based on the available evidence, there appears to be no role for albumin (and perhaps HES) in patients with TBI as evidenced by increased mortality in this patient population, especially in the setting of severe TBI. While the underlying research is problematic, the use of HES in patients with blunt trauma appears non-superior to crystalloids and possibly deleterious as demonstrated most consistently by elevated transfusion requirements likely secondary to coagulopathy. While there may be a role for small volumes of HES during early resuscitation following penetrating trauma, especially when faced with delayed transport, there is not enough evidence to recommend its use in a hospital setting during initial resuscitation, intraoperative care, or in the ICU thereafter, especially when coupled with an established poor safety profile in critically ill patients.

Compliance with Ethics Guidelines

Conflict of Interest Craig Jabaley and Roman Dudaryk declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. Crit Care. 2005;9(Suppl 5):S1–9.
2. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma. 1995;38(2):185–93.
3. Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg. 1998;186(5):528–33.
4. Hoyt DB, Bulger EM, Knudson MM, Morris J, Ierardi R, Sugerman HJ, et al. Death in the operating room: an anlysis of a multi-center experience. J Trauma. 1994;37(3):426–32.
5. Finfer S, Liu B, Taylor C, Bellomo R, Billot L, Cook D, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. Crit Care. 2010;14(5):R185.
6. Graham T. Liquid diffusion applied to analysis. Phil Trans R Soc Lond. 1861;151:183–224.
7. Michel CC. Starling: the formulation of his hypothesis of microvascular fluid exchange and its significance after 100 years. Exp Physiol. 1997;82(1):1–30.
8. Hu XP, Weinbaum S. A new view of Starling's hypothesis at the microstructural level. Microvasc Res. 1999;58(3):281–304.
9. Köhler M, Kaufmann I, Briegel J, Jacob M, Goeschl J, Rachinger W, et al. The endothelial glycocalyx degenerates with increasing sepsis severity. Crit Care. 2001;15(S3):P22.
10. Nelson A, Berkestedt I, Schmidtchen A, Ljunggren L, Bodelsson M. Increased levels of glycosaminoglycans during septic shock: relation to mortality and the antibacterial actions of plasma. Shock. 2008;30(6):623–7.
11. Jacob M, Rehm M, Loetsch M, Paul JO, Bruegger D, Welsch U, et al. The endothelial glycocalyx prefers albumin for evoking shear stress-induced, nitric oxide-mediated coronary dilatation. J Vasc Res. 2007;44(6):435–43.
12. Becker BF, Chappell D, Bruegger D, Annecke T, Jacob M. Therapeutic strategies targeting the endothelial glycocalyx: acute deficits, but great potential. Cardiovasc Res. 2010;87(2):300–10.
13. Wiggers CJ. The present status of the shock problem. Physiol Rev. 1942;22:74–123.
14. Shires T, Coln D, Carrico J, Lightfoot S. Fluid therapy in hemorrhagic shock. Arch Surg. 1964;88:688–93.
15. Bickell WH. Are victims of injury sometimes victimized by attempts at fluid resuscitation? Ann Emerg Med. 1993;22(2):225–6.
16. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105–9.
17. Kwan I, Bunn F, Roberts I, Committee WHOP-HTCS. Timing and volume of fluid administration for patients with bleeding. Cochrane Database Syst Rev. 2003;3(3):CD002245.
18. Curry N, Hopewell S, Doree C, Hyde C, Brohi K, Stanworth S. The acute management of trauma hemorrhage: a systematic review of randomized controlled trials. Crit Care. 2011;15(2):R92.
19. • Guidry C, Gleeson E, Simms ER, Stuke L, Meade P, McSwain NE, Jr. et al. Initial assessment on the impact of crystalloids versus colloids during damage control resuscitation. J Surg Res. 2013;185(1):294–9. *This retrospective study suggests a role for low-volume initial resusciation with HES as an adjunt in patients requiring damage control surgery.*
20. Hogan JJ. The intravenous use of colloidal (gelatin) solutions in shock. JAMA. 1915;64(9):721–6.
21. American doctor to save Germans. The New York Times. 1915/7/28.
22. Bayliss WM. Gum injections in "shock". J Nerv Ment Dis. 1919;50(1):88.
23. Van der Kloot W. William Maddock Bayliss's therapy for wound shock. Notes Rec Roy Soc. 2010;64:271–86.
24. Le Gal YM. A review of the history of blood replacement from the 17th to the 20th centuries. Rev Surg. 1975;32(4):229–39.
25. Heckel GP, Erickson CC, Yuile CL, Knutti RE. Blood plasma proteins as influenced by intravenous injection of gum acacia. J Exp Med. 1938;67(3):345–59.

26. Hecht G, Weese H. Periston, ein neuer blutflüssigkeitsersatz. Münchener Medizinische Wochenschrift. 1943;90:11.
27. National Research Council, editor. Meeting of Subcommittee on Shock Fiscal Year, Committee on Blood and Related Problems, Division of Medical Sciences. Annual Report—National Academy of Sciences—Fiscal Year 1952–1953; 1958; Washington, DC.
28. Johnson GS, Blalock A. Experimental shock IX: a study of the effects of the loss of whole blood, of blood plasma and of red blood cells. Arch Surg. 1931;22(4):626–37.
29. Cohn EJ. The history of plasma fractionation. In: Andrus, editor. Advances in military medicine. Boston: Little, Brown & Co; 1948.
30. Peters T Jr. Historical perspective. All about albumin: biochemistry, genetics, and medical applications. San Diego: Academic Press; 1996. p. 1–8.
31. Grönwall A. Dextran and its use in colloidal infusion solutions. Uppsala: Almquist and Wiksell, Printers & Publishers; 1957.
32. Artz CP, Howard JM, Frawley JP. Clinical observations on the use of dextran and modified fluid gelatin in combat casualties. Surgery. 1955;37(4):612–21.
33. Howard JM, Teng CT, Loeffler RK. Studies of dextrans of various molecular sizes. Ann Surg. 1956;143(3):369–72.
34. Vickery AL. The fate of dextran in tissues of the acutely wounded; a study of the histologic localization of dextran in tissues of Korean battle casualties. Am J Pathol. 1956;32(2):161–83.
35. Fishman AP. Shock lung: a distinctive nonentity. Circulation. 1973;47(5):921–3.
36. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. Crit Care Med. 1999;27(1):200–10.
37. Schierhout G, Roberts I. Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials. Brit Med J. 1998;316(7136):961–4.
38. Ertmer C, Rehberg S, Van Aken H, Westphal M. Relevance of non-albumin colloids in intensive care medicine. Best Pract Res Clin Anaesthesiol. 2009;23(2):193–212.
39. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet. 1996;348(9042):1620–2.
40. Schortgen F, Lacherade JC, Bruneel F, Cattaneo I, Hemery F, Lemaire F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet. 2001;357(9260):911–6.
41. Jonville-Bera AP, Autret-Leca E, Gruel Y. Acquired type I von Willebrand's disease associated with highly substituted hydroxyethyl starch. N Engl J Med. 2001;345(8):622–3.
42. Gandhi SD, Weiskopf RB, Jungheinrich C, Koorn R, Miller D, Shangraw RE, et al. Volume replacement therapy during major orthopedic surgery using Voluven (hydroxyethyl starch 130/0.4) or hetastarch. Anesthesiology. 2007;106(6):1120–7.
43. Jungheinrich C, Scharpf R, Wargenau M, Bepperling F, Baron JF. The pharmacokinetics and tolerability of an intravenous infusion of the new hydroxyethyl starch 130/0.4 (6%, 500 mL) in mild-to-severe renal impairment. Anesth Analg. 2002;95(3):544–51.
44. Gallandat Huet RC, Siemons AW, Baus D, van Rooyen-Butijn WT, Haagenaars JA, van Oeveren W et al. A novel hydroxyethyl starch (Voluven) for effective perioperative plasma volume substitution in cardiac surgery. Can J Anaesth. 2000;47(12):1207–15.
45. Wilkes MM, Navickis RJ. The Boldt affair: a quandry for meta-analysts. Anesthesiology News. 2013 April.
46. •• Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database of Systematic Reviews. 2013. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000567.pub6/abstract. *This excellent Cochrane Review summarizes the findings concerning the role of colloids in trauma, burn, and surgical patients patients and recommends against their routine use.*
47. Gattas DJ, Dan A, Myburgh J, Billot L, Lo S, Finfer S. Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: an updated systematic review and meta-analysis. Anesth Analg. 2012;114(1):159–69.
48. • Perner A, Haase N, Guttormsen AB, Tenhunen J, Klemenzson G, Aneman A et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med. 2012;367(2):124–34. *The 6S trial demonstrated an increase in 90 day mortality and need for renal replacement therapy in septic patients treated with HES.*
49. • Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901–11. *The CHEST trial linked HES use in an ICU setting with worsened renal outcomes but no difference in mortality.*
50. Guidet B, Martinet O, Boulain T, Philippart F, Poussel JF, Maizel J, et al. Assessment of hemodynamic efficacy and safety of 6 % hydroxyethylstarch 130/0.4 vs. 0.9 % NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care. 2012;16(3):R94.
51. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008;358(2):125–39.
52. Chappell D, Jacob M. Twisting and ignoring facts on hydroxyethyl startch is not very helpful. Scand J Trauma Resusc Emerg Med. 2013;21:85.
53. Chappell D, Jacob M. Hydroxyethyl starch: the importance of being earnest. Scand J Trauma Resusc Emerg Med. 2013;21:61.
54. United States Food and Drug Administration. FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings. 2013.
55. Shires GT, Carrico CJ, Baxter CR, Giesecke AH Jr, Jenkins MT. Principles in treatment of severely injured patients. Adv Surg. 1970;4:255–324.
56. Cervera AL, Moss G. Progressive hypovolemia leading to shock after continuous hemorrhage and 3:1 crystalloid replacement. Am J Surg. 1975;129(6):670–4.
57. Annane D, Siami S, Jaber S, Martin C, Elatrous S, Declere AD, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. JAMA. 2013;310(17):1809–17.
58. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med. 2004;350(22):2247–56.
59. • Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero M et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med. 2014;370(15):1412–21. *The most recent large RCT examining the role of albumin in patients with septic shock found no survival benefit.*
60. Wilkes MM, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. Ann Thorac Surg. 2001;72(2):527–33; discussion 34.
61. Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. J Thorac Cardiovasc Surg. 2012;144(1):223–30.
62. Kozek-Langenecker SA, Jungheinrich C, Sauermann W, Van der Linden P. The effects of hydroxyethyl starch 130/0.4 (6%) on blood loss and use of blood products in major surgery: a pooled analysis of randomized clinical trials. Anesth Analg. 2008;107(2):382–90.
63. Haase N, Perner A, Hennings LI, Siegemund M, Lauridsen B, Wetterslev M et al. Hydroxyethyl starch 130/0.38–0.45 versus

crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis. Brit Med J. 2013;346:f839.
64. Hartog CS, Reuter D, Loesche W, Hofmann M, Reinhart K. Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. Intensiv Care Med. 2011;37:1725–37.
65. Cochrane Injuries Group Albumin R. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Brit Med J. 1998; 317(7153):235–40.
66. Yamey G. Albumin industry launches global promotion. Brit Med J. 2000;320(7234):533.
67. Roberts I, Edwards P, McLelland B. Use of human albumin in UK fell substantially when systematic review was published. Brit Med J. 1999;318(7192):1214.
68. Wilkes MM, Navickis RJ. Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med. 2001;135(3):149–64.
69. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg. 2003;237(3):319–34.
70. Myburgh J, Cooper DJ, Finfer S, Bellomo R, Norton R, Bishop N, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357(9):874–84.
71. Cooper D, Myburgh J, Heritier S, Finfer S, Bellomo R, Billot L, et al. Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? J Neurotrauma. 2013;30(7):512–8.
72. Butler FK Jr, Hagmann J, Butler EG. Tactical combat casualty care in special operations. Mil Med. 1996;161(Suppl):3–16.
73. Butler FK Jr, Hagmann JH, Richards DT. Tactical management of urban warfare casualties in special operations. Mil Med. 2000; 165(4 Suppl):1–48.
74. The Committee on Tactical Combat Casualty Care: 2002. Military Medicine. In: PreHospital Trauma Life Support. St. Louis, MO: Elsevier Mosby; 2004. pp. 374–408.
75. Champion HR. Combat fluid resuscitation: introduction and overview of conferences. J Trauma. 2003;54(5 Suppl):S7–12.
76. Holcomb JB. Fluid resuscitation in modern combat casualty care: lessons learned from Somalia. J Trauma. 2003;54(5 Suppl): S46–51.
77. Pearce FJ, Lyons WS. Logistics of parenteral fluids in battlefield resuscitation. Mil Med. 1999;164(9):653–5.
78. McSwain NE, Champion HR, Fabian TC, Hoyt DB, Wade CE, Eastridge BJ, et al. State of the art of fluid resuscitation 2010: prehospital and immediate transition to the hospital. J Trauma. 2011;70(5 Suppl):S2–10.
79. Ogilvie MP, Pereira BM, McKenny MG, McMahon PJ, Manning RJ, Namais N, et al. First report on safety and efficacy of hetastarch solution for initial fluid resuscitation at a Level 1 trauma center. J Am Coll Surg. 2010;210(5):870–80.
80. Ryan ML, Ogilvie MP, Pereira BM, Gomez-Rodriguz JC, Livingstone AS, Proctor KG. Effect of hetastarch bolus in trauma patients requiring emergency surgery. J Spec Oper Med. 2012; 12(3):57–67.
81. • Lissauer ME, Chi A, Kramer ME, Scalea TM, Johnson SB. Association of 6% hetastarch resuscitation with adverse outcomes in critically ill trauma patients. Am J Surg. 2011;202(1):53–8. *This retrospective study of HES in trauma patients admitted to the ICU demonstrated multiple negative outcomes when compared to resuscitation with saline*.
82. Nagy KK, Davis J, Duda J, Fildes J, Roberts R, Barrett J. A comparison of pentastarch and lactated Ringer's solution in the resuscitation of patients with hemorrhagic shock. Circ Shock. 1993;40(4):289–94.
83. Younes RN, Yin KC, Amino CJ, Itinoshe M, Rocha e Silva M, Birolini D. Use of pentastarch solution in the treatment of patients with hemorrhagic hypovolemia: randomized phase II study in the emergency room. World J Surg. 1998;22(1):2–5.
84. • James MF, Mitchell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating rauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Brit Med J. 2011;107(5):693–702. *As the first published randomized trial of hetastarch in trauma patients, this study suggests a possible role for HES in penetrating trauma despite multiple design flaws*.
85. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Re: Hydroxyethyl starch in patients with trauma, author's reply. Brit Med J. 2012;108(2):322–4.
86. ISRCTN Register. ISRCTN 42061860, A trial of crystalloid versus colloid fluid solutions for the resuscitation of patients with severe injuries. London, UK. 2009. http://www.controlled-trials.com/ISRCTN42061860/42061860. Accessed 18 Apr 2014.
87. National Library Of Medicine. Identifier NCT00890383, Colloids in Severe Trauma (CIST). Bethesda, MD. 2009. http://clinicaltrials.gov/ct2/show/study/NCT00890383. Accessed 18 Apr 2014.

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Fluid management in patients with trauma: Restrictive versus liberal approach

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Abstract

Trauma is a leading cause of death worldwide, and almost 30% of trauma deaths are due to blood loss. A number of concerns have been raised regarding the advisability of the classic principles of aggressive crystalloid resuscitation in traumatic hemorrhagic shock. Some recent studies have shown that early volume restoration in certain types of trauma before definite hemostasis may result in accelerated blood loss, hypothermia, and dilutional coagulopathy. This review discusses the advances and changes in protocols in fluid resuscitation and blood transfusion for treatment of traumatic hemorrhage shock. The concept of low volume fluid resuscitation also known as permissive hypotension avoids the adverse effects of early aggressive resuscitation while maintaining a level of tissue perfusion that although lower than normal, is adequate for short periods. Permissive hypotension is part of the damage control resuscitation strategy, which targets the conditions that exacerbate hemorrhage. The elements of this strategy are permissive hypotension, minimization of crystalloid resuscitation, control of hypothermia, prevention of acidosis, and early use of blood products to minimize coagulopathy.

Keywords: Damage control resuscitation, fluid resuscitation, massive transfusion protocol, permissive hypotension

Introduction

Globally, injuries contribute to around 10% of total deaths and 15% of disability-adjusted life-years.[1] Recent studies suggest that injuries contribute to 13-18% of total deaths in India. Road traffic injuries (RTIs) place a huge burden on the health sector in terms of prehospital care, acute care, and rehabilitation.[1] According to WHO, RTIs are the sixth leading cause of deaths in India with a greater share of hospitalizations, deaths, disabilities and socioeconomic losses in young and middle-age populations. Most of the deaths occur due to poor decision and inappropriate interventions. An estimated 10-20% of these deaths are potentially preventable with better control of bleeding. Early hemorrhage within 6 h after incurring an injury emerged as the biggest cause of preventable deaths. This has led trauma teams to investigate whether the change in practice could help reduce early mortality after severe trauma.[2]

For the past four decades, the standard approach to the trauma victim, who is hypotensive from presumed hemorrhage has been to transfuse large volumes of fluid as early and as rapidly as possible. The goals of this treatment strategy are rapid restoration of intravascular volume and vital signs toward normal and maintenance of vital organ perfusion. High volume IV fluid for hemodynamic instability has been the accepted standard in most prehospital care systems like advanced trauma life support system (ATLS). The

most recent laboratory studies and clinical trials evaluating the efficacy of these guidelines however suggest that in the setting of uncontrolled hemorrhage, aggressive fluid resuscitation may be harmful, resulting in increased hemorrhagic volume and subsequently greater mortality.[3]

To devise a strategy for resuscitation certain questions needs to be answered.

- What is the risk of hypovolemia in trauma patients?
- What is resuscitation injury?
- What strategies of fluid resuscitation are available?
- Liberal versus restrictive
- What are various recommendations from the literature?

We need to understand the pathophysiology of trauma and hemorrhagic shock. It may be defined as a life threatening condition characterized by inadequate delivery of oxygen to vital organs in relation to their metabolic requirements.[4] A systolic blood pressure (SBP) of 90 mmHg is commonly used to define both hypotension and shock; however, oxygen delivery depends on cardiac output rather than blood pressure. Homeostasis with peripheral vasoconstriction acts to preserve blood pressure even as circulatory volume is lost. The relation between cardiac output and blood loss is ill-defined, and the relationship becomes evident only when more than half of circulating volume is lost, or the loss is rapid. Many patients will maintain their pulse and blood pressure even after massive blood loss and tissue hypoxia. This condition is termed as a cryptic shock and is associated with increased mortality.[5]

Resuscitation Injury

Another parameter that needs to be understood is resuscitation injury. In the setting of trauma, capillary permeability increases, leading to a loss of intravascular fluid into the interstitial space. Moreover, acidosis that results from significant trauma impairs cardiac function.[6] Treating these patients with a large volume of crystalloids can lead to cellular swelling and resulting dysfunction.[6] Fluid causes dilutional coagulopathy, clot disruption from increased blood flow, decreased blood viscosity and interstitial edema. There is increased risk of acute respiratory distress syndrome and multi-organ failure. Large volume crystalloid resuscitation causes gastrointestinal and cardiac complications,[5] increased extremity compartment pressures[7] and coagulation disturbances. Abdominal compartment syndrome is clearly proven to be a result of large volume crystalloid resuscitation.[8] Secondary abdominal compartment syndrome occurs in patients without any underlying abdominal injury, has mortality >50% and is clearly linked to over aggressive fluid resuscitation strategies.[8]

Pathophysiology of Hypovolemic Micro-circulation

Hypovolemia and blood loss lead to inadequate perfusion of micro-circulation that result in insufficient oxygen availability to meet the needs of mitochondrial oxidative phosphorylation. Adequate micro-circulation relies on the function of the different components of micro-circulation. Red and white blood cells, endothelial cells and smooth muscle cells have to function in close harmony to ensure adequate micro-circulatory blood flow to transport oxygen to the tissues. The function of these components is affected by hypovolemia. Administration of fluids to correct hypovolemia may modulate micro-circulatory function by various mechanisms. The flow is increased by enhanced filling of the vasculature that generates forcing pressure and promotes micro-circulatory perfusion. Fluids also modify the hemorheology of blood by decreasing the viscosity that additionally promotes blood flow. However, excessive hemodilution can cause shunting of the micro-circulation and impair regional tissue oxygenation. This effect can differ among the different organ systems.[9]

Coagulation and Trauma

Coagulation disorders in trauma have a complex pathophysiology including activation or dysfunction of fibrin generation or both, platelet and endothelium dysfunction, relative inhibition of stable clot formation by anticoagulant and fibrinolytic pathways and either consumption or inhibition of coagulation proteases.

Fluid shifts associated with blood loss, crystalloid infusion and transfusion of packed red blood cells (RBC's) contributes to dilutional coagulopathy. Hypothermia and acidosis also contributes to coagulopathy and continued blood loss. Shock following acute blood loss or RBC's appears to be the most important factor in the development of coagulopathy. Hess *et al.*[10] have suggested in their review six main precipitants of coagulopathy in trauma — tissue trauma, shock, hemodilution, hypothermia, acidemia and inflammation.

The alternate strategy to the early resuscitation is limited resuscitation or hypotensive resuscitation. Two slightly different strategies have been advanced to prevent clot disruption and dilutional coagulopathy. The first is delayed resuscitation, where fluid is withheld until bleeding is definitively controlled. The second is permissive hypotension, where fluid is given, but the resuscitative endpoint is something less than normotension.[11] This approach provides a mechanism for avoiding the detrimental effects associated with early aggressive resuscitation. Permissive hypotension is a term used to describe the use of restricted fluid therapy especially in trauma patients that increases systemic blood pressure without reaching normotension. This implies that maintaining perfusion although decreased from the normal physiological range, is adequate for short periods. The concept does not exclude therapy by means of intravenous fluids; inotropes or vasopressor, the only restriction is to avoid completely normalizing blood pressure in a context where blood loss may be enhanced.[12]

Timings and Goals of Resuscitation from Hemorrhagic Shock

Liberal versus restrictive approach

Advocates of aggressive crystalloid resuscitation suggest that the theoretical benefits of normalizing or even super normalizing blood pressure and oxygen delivery are clear. These benefits include repayment of oxygen debt, clearance of acidosis, and correction of extracellular fluid deficit. However, more recent evidence (primarily in models of uncontrolled hemorrhage) suggests that premature or aggressive resuscitation may lead to dislodging of soft clots and dilutional coagulopathy, which results in increased hemorrhage and mortality.[13]

A recent study reported that overly aggressive fluid treatment accelerated hepatocellular injury while another suggested that slower rates of fluid resuscitation led to improvements in cell mediated immunity.[14] Numerous studies have shown that immediate fluid resuscitation caused increases in the rate, volume, and duration of hemorrhage. Before discussing human data on restrictive resuscitation strategies, it must be noted that all strategies that permit hypotension are absolutely contraindicated in patients with traumatic brain injury (TBI). It has been shown that even a single episode of hypotension causes a doubling of mortality in this patient population.

In the presence of uncontrolled hemorrhage in patients with concurrent TBI, prevention of secondary brain injury from hypotension is crucial as a SBP <90 mmHg is associated with poor outcomes. Infuse small aliquots of fluid (100-200 ml) to maintain SBP above 90 mmHg (Grade I evidence). Concept of permissive hypotension should be carefully considered in the elderly patients and are relatively contraindicated in patients with chronic arterial hypertension, carotid stenosis, angina pectoris and compromised renal function.

Rethinking of aggressive fluid resuscitation followed the publication of famous “Mattox trial” in 1994 by Bickell *et al.*[15] The investigators performed a prospective, single center trial comparing immediate and delayed fluid resuscitation in 598 adults with penetrating torso injuries. All patients presenting had a prehospital SBP of <90 mmHg. A total 203 of 289 patients (70%) who received delayed fluid resuscitation survived compared with 193 of 309 patients (62%) who received immediate fluid resuscitation ($P = 0.4$). The number of patients having one or more postsurgical complications was lower in the delayed fluid resuscitation group versus those receiving immediate fluid resuscitation: About 23% versus 30% respectively. Numerous studies before and since this study have failed to demonstrate a survival benefit for aggressive fluid resuscitation before mechanical stabilization of the injury. There is also evidence to suggest that restoring normal or near normal blood pressure using fluid resuscitation before surgery may even worsen survival.

In a study undertaken in 2002 by Dutton *et al.*, 110 patients with hemorrhagic shock were randomized into two groups with target SBP >100 mmHg and target SBP of 70 mmHg. Fluid therapy was targeted to this end point. They used a technique of 250-500 ml boluses to treat hypotensive values. Unfortunately, they found that the blood pressure tended to fluctuate with the boluses, making it hard to accurately maintain the desired value. As a result, for the 110 patients they randomized, the average SBP was 100 mgHg in the restricted protocol and 114 mmHg in the standard cohort ($P < 0.001$). Survival was equal at 92.7% with four deaths in each group.[16]

Sampalis *et al.*[17] reviewed the outcome of 217 trauma patients who had received intravenous fluids and compared them with 217 controls who received no-fluids. Correction was made for gender, age, mechanism for injury and injury severity score. Patients who received onsite fluid resuscitation had a higher mortality than the control group, particularly when fluid resuscitation was combined with prolonged prehospital times. They compared prehospital times of <30 min with time >30 min. In one group, the use of onsite IV fluid replacement provides no association with a significant increase in mortality.

In 1986, Blair *et al.*[18] reported that the incidence of rebleeding was decreased in patients with gastrointestinal hemorrhage for whom early transfusion was withheld ($P < 0.01$). With a relative paucity of human data, a Cochrane review[19] came to the conclusion that there was no evidence for or against early volume resuscitation in uncontrolled hemorrhage. This study did not prefer one colloid over another and hypertonic crystalloid over isotonic crystalloid.

Cochrane review was done on timing and volume of fluid administration for patients with bleeding to assess the effects of early versus delayed; larger versus smaller volume of fluid administration, in trauma patients with bleeding. In this review, there is no evidence from randomized controlled trials for or against early or larger volume of intravenous fluid administration in uncontrolled hemorrhage. The review concluded that the uncertainty continues regarding best fluid administration strategy in bleeding trauma patients. Further, randomized controlled trials are needed to establish the most effective fluid resuscitation strategy.

A study done by Turner *et al.*,[20] in 1309 hypotensive trauma patients randomized to receive fluids or no-fluids in the prehospital period revealed 10.4% mortality in early fluid administration group versus 9.8% in delayed/no fluid group. It recommended that rather than concentrating on fluid protocols, ambulance services should avoid unnecessary delays and speed up transfer to definitive care in the hospital.

A study by Anne Morrison *et al.*[21] showed that hypotensive resuscitation strategy reduces transfusion requirement and severe postoperative coagulopathy in trauma with hemorrhagic shock. It showed that hypotensive resuscitation is a safe strategy in trauma population and hypotensive resuscitation to minimum intraoperative mean arterial pressure (MAP) of 50 mmHg does not increase 30 days mortality as compared to target MAP of 65 mmHg. It reduces the risk of early postoperative mortality of coagulopathy bleeding and does not increase the length of hospital/intensive care unit (ICU) stay.

Emergency Department Evaluation of a Patient in Shock

When the trauma patients arrive at triage, they must be rapidly assessed for either being in shock or at risk of shock. Trauma patients should have their airway, breathing and circulation addressed immediately followed by trauma team activation and controlling the source of bleeding and localizing by focused assessment sonography in trauma (FAST)/X-ray chest [Table 1].

Damage Control Resuscitation[27]

The coagulopathy of trauma is already present in many patients on their arrival to the emergency, and it impacts management. The treatment of coagulopathy in hemorrhagic shock is no longer the responsibility of just the surgeon and the intensivist but initiating the treatment is also within the emergency clinician's purview. This treatment is an essential part of what has come to known as damage control resuscitation (DCR).[22,23,24]

The term “lethal triad” is used to describe the mutually perpetuating combination of acute coagulopathy, hypothermia, and acidosis seen in exsanguinating trauma patients.[25] Hypo-perfusion leads to decreased oxygen delivery, a switch to anaerobic metabolism, lactate production, and metabolic acidosis. Anaerobic

metabolism limits endogenous heat production, exacerbating hypothermia caused by exposure and injudicious administration of cold resuscitation fluids and blood. Large, well-conducted retrospective studies have shown that the core temperature of <35°C on admission is an independent predictor of mortality after major trauma.[26]

An understanding of the mechanism of coagulopathy, acidosis, and hypothermia "Lethal Triad" forms the basis of DCR. DCR addresses all the three components of the Lethal Triad and integrates the permissive hypotension, hemostatic resuscitation and damage control surgery.[27] Aim is to minimize hypovolemic shock diagnosed by triad of pattern recognition — cold clammy skin, weak or absent radial pulse and abnormal mental status in that acidosis, hypotension and hypothermia need to be addressed too. Acidosis with the base deficit of more than 6 mmol/L is a predominant physiological defect resulting from persistent hypo-perfusion. pH of <7.2 is associated with decreased contractility and cardiac output, vasodilatation, hypotension, bradycardia, dysarrhythmias and decreased blood flow to liver and kidney. Hypothermia is associated with high mortality. If the temperature is <96.50°F hypocoagulability occurs. However, damage control approach is suitable for only selected group of patients. Asensio *et al.*[27] identified preoperatively characteristics predictive of "exsanguinating syndrome" in which a damage control would be appropriate [Table 2].

Components of Damage Control Resuscitation

Permissive hypotension

The aim is to allow a subnormal blood pressure to minimize hemorrhagic blood loss. For uncontrolled hemorrhage in the absence of TBI, target resuscitation to SBP of 7-90 mmHg, normal mentation and palpable peripheral pulses (level of evidence III). Blood should allow sufficient oxygen delivery to tissues that is ensured by monitoring serum lactate levels and central venous oxygen saturation. There is no study in pediatrics to support its use.

Hemostatic resuscitation

The term denotes the very early use of blood and blood products as primary resuscitation fluids to treat intrinsic acute traumatic coagulopathy and to prevent the development of dilutional coagulopathy. It is initiated within minutes of arrival in the emergency department. First resuscitation is limited to keep blood pressure at 90 mmHg, preventing renewed bleeding from recently clotted vessels. Secondly, intravascular volume restoration is accomplished using thawed plasma a primary resuscitation fluid in at least 1:1 ratio with packed red blood cells (PRBC). Causalities who require continued resuscitation, massive transfusion protocol (MTP) is activated with delivery of 6 units of plasma, 6 units of PRBCs and 10 units of cryoprecipitate. Ruskin *et al.*[28] showed that deaths from trauma significantly decreased after introduction of MTP.

Massive transfusion however may cause hypocalcemia, hyperkalemia, hypomagnesemia, acid base disturbances, hypothermia, thrombocytopenia, and coagulopathy. Recent studies indicate that packed red cells replacement along with fresh frozen plasma (FFP) and platelet concentrates early in trauma management prevents dilutional effects and markedly improves the coagulopathic bleeding in trauma patients. The aggressive hemostatic resuscitation should be combined with equally aggressive control of bleeding. Tranexamic acid, an antifibrinolytic agent, is to be given to all patients with uncontrolled bleeding who required blood transfusion.[13] As per CRASH-2 trial[29] in 2010 for evaluation of the role of tranexamic acid, 20,000 trauma patients were randomized to receive either tranexamic acid or control. Tranexamic acid significantly reduced the risk of death (odds ratio [OR]: 0.91 [0.85-0.97], $P = 0.0035$) and death from hemorrhage (OR: 0.85 [90.76-0.96], $P < 0.001$) without any increase in thromboembolic complication.

Damage control surgery

Damage control surgery is defined as the planned temporary sacrifice of normal anatomy to preserve the vital physiology. This is a concept in which the initial surgery becomes part of the resuscitation process rather than part of the curative process.[30,31] It consists of 3 parts including the initial abbreviated laparotomy, ICU resuscitation and subsequent reoperation for definitive resuscitation [Figure 1].[32]

Damage control surgery is a surgical strategy aimed at restoring normal physiology rather than anatomical integrity. Only when the patient has become physiologically stable is the final therapeutic surgery embarked on. This process serves to limit the physiological exposure to an unstable environment, allowing better resuscitation and outcome in the critically ill trauma patients.

Multidisciplinary approach to the management of critically injured, updated European guidelines[33] recommends [Figure 2]:

- Time elapsed between injury and operation should be minimized for patients in need of urgent surgical bleeding control (Grade IA).
- Patients presenting with hemorrhagic shock and an indentified source of bleeding should undergo an immediate bleeding control procedure unless initial resuscitation measures are successful (Grade IB).
- Early imaging (FAST or computed tomography) for detection of free fluid in patients with suspected torso trauma (Grade IB). If FAST is positive, it should be followed by immediate intervention.
- A target SBP of 80-100 mmHg until major bleeding is stopped in the initial phase without TBI (Grade IC). Low volume approach is contraindicated in TBI as adequate perfusion pressure is crucial to ensure tissue oxygenation of injured central nervous system.
- Target MAP of 65 mmHg or more, in controlled hypotensive resuscitation.
- Adjunct tourniquet use to stop life-threatening bleeding from open extremity injuries in the presurgical setting.
- Initial normoventilation of trauma patients if there are no signs of imminent cerebral herniation. A low partial pressure of arterial carbon dioxide on admission to the emergency room is associated with a worse outcome in trauma patients with TBI. Hyperventilation and hypocapnia cause intense vasoconstriction with decreased cerebral blood flow and impaired tissue perfusion.
- Hemorrhagic shock with identified source of bleeding — initiate immediate bleeding control procedure.
- Serum lactate and base deficit measurement to estimate and monitor extent of bleeding and shock (Grade IB). Serum lactate is diagnostic parameter and prognostic marker of hemorrhagic shock. The amount of lactate produced by anaerobic glycolysis is an indirect marker of oxygen debt, tissue hypo-perfusion and the severity of hemorrhagic shock. Base deficit gives indirect estimation of acidosis due to impaired perfusion. Repeated lactate determinations represent a reliable prognostic index for patients with circulatory shock.
- DCR should be employed in severely injured patient presenting with deep hemorrhagic shocks, signs of ongoing bleeding and coagulopathy, hypothermia, acidosis, inaccessible major anatomical injury.
- Crystalloid should be applied initially for bleeding trauma patients (Grade IB). Hypertonic saline (HTS) to be considered for hemodynamically unstable patients (Grade 2B). Addition of colloid to be considered within the prescribed limits for each solution in hemodynamically unstable patients (Grade 2C).
- Early FFP in patients with massive bleeding (Grade IB). Platelets to be administered to maintain the count above 50×10^9/L (Grade IC). However, maintain the count above 100×10^9/L in patients with multiple trauma who are severely bleeding or have traumatic brain trauma (Grade 2C).
- Tranexamic acid 10-15 mg/kg followed by infusion of 1-5 mg/kg/h (Grade IB).
- Target hemoglobin of 7-9 gm% (Grade IC).
- Monitoring of ionized calcium during massive transfusion (Grade IC). Calcium chloride to be administered if ionized calcium levels are low or electrocardiographic changes suggests hypocalcemia (Grade 2C).

Characteristics of Optimal Resuscitation Fluid

As stated by Tremblay *et al.*[34] that "… the optimal fluid for resuscitation would combine the volume expansion and oxygen carrying capacity of blood, without the need for cross-matching or the risk of disease transmission. In addition, it would restore and maintain the normal composition and distribution of body fluid compartments." Taking this one step further, the ideal fluid would combine all of those things with positive immunologic and coagulation effects and be durable, portable, and cheap. None of the fluid options currently available comes close to this ideal. Standard trauma resuscitation as defined by the ATLS course includes infusion of ringer lactate solution,[35] which is a racemic mixture containing two stereo-isomers of lactate D-lactate and L-lactate. Normal saline is also frequently used with lactated ringer for resuscitation in hemorrhagic shock, but it has been associated with hyperchloremic acidosis, when given in large volumes.[13]

Hypertonic saline and hypertonic saline dextran solutions (HSD) have also been used as a treatment for raised intra-cranial pressure and early treatment for TBI. Early administration of HSD can lead to improved serum biomarkers of brain injury. But at this time, there is no evidence to suggest that either HTS or HSD provide significant benefit in the early treatment of patients with TBI.[13]

Traditionally there has been no role of colloids in trauma resuscitation due to associated side effects. Gelatins have been associated with anaphylaxis and significant hypernatraemia. They also cause paradoxical hypotension due to release of bradykinin by contaminants.[35] Coagulopathy is a common complication of hemorrhagic shock. Resuscitation associated hemodilution may alter hemostasis by lowering the concentration of clotting proteins. Use of crystalloids has been thought to be without negative effect on coagulation except for that attributable to hemodilution. Crystalloids have no specific adverse effects on renal function except that they may not restore blood volume adequately.[36] However, colloids have adverse effects on renal function. In patients with excessive fluid deficits, glomerular filtration of hyperoncotic colloids (dextrans, 10% hydroxyl ethyl starch [HES], 20% albumin) may cause a hyperviscous urine and stasis of the tubular flow resulting in obstruction of tubular lumen.[36,37] Gelatins have no significant damaging effect on the kidneys.[36,37]

The controversy regarding the use of crystalloids versus colloids for resuscitation has been in debate for last so many years. A recent Cochrane database analysis on crystalloids versus colloids published in 2013 that the resuscitation using colloids compared with crystalloids reduces the risk of death in patients with trauma, burns or following surgery. The use of HES may increase mortality.[38] Cochrane review concluded that since colloid use is not associated with improved survival, and they are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.[39] Further clinical trials of colloid use need to justify carefully the potential for patient benefit.

Standard approach to trauma victims has been to infuse large volumes of isotonic crystalloids as early and rapidly as possible. Most efficient solution for use is still under debate. The various options available are summarized in Table 3.

Conclusion

Debate continues regarding the strategy of fluid management in trauma. Hemorrhagic shock remains a leading cause of morbidity and mortality worldwide. Time-consuming procedures in the field should be avoided, and rapid transport to definitive care should be aimed at. Fluid choice has not been shown to affect the outcome in trauma, however large volume of the crystalloid resuscitation need to be avoided. In the absence of TBI, target SBP of 70-90 mmHg, normal mentation and peripheral pulses in case of uncontrolled hemorrhage should be aimed at. Normotension should be the aim in the presence of TBI. Tranexamic acid should be given to all the patients with penetrating trauma who need transfusion. MTP with fixed ratios should be given. Patients with penetrating trauma for whom definitive care is immediately available may benefit from damage control surgery. While DCR requires further study, the early literature seems to be promising.

Footnotes

Source of Support: Nil

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References

1. Gururaj G. Road traffic deaths, injuries and disabilities in India: Current scenario. Natl Med J India. 2008;21:14–20. [PubMed: 18472698]

2. Holcomb JB, McMullin NR, Pearse L, Caruso J, Wade CE, Oetjen-Gerdes L, et al. Causes of death in U.S. Special Operations Forces in the global war on terrorism: 2001-2004. Ann Surg. 2007;245:986–91. [PMCID: PMC1876965] [PubMed: 17522526]

3. Stern SA. Low-volume fluid resuscitation for presumed hemorrhagic shock: helpful or harmful? Curr Opin Crit Care. 2001;7:422–30. [PubMed: 11805545]

4. Strehlow MC. Early identification of shock in critically ill patients. Emerg Med Clin North Am. 2010;28:57–66. vii. [PubMed: 19945598]

5. Cotton BA, Guy JS, Morris JA, Jr, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock. 2006;26:115–21. [PubMed: 16878017]

6. Lang F, Busch GL, Ritter M, Völkl H, Waldegger S, Gulbins E, et al. Functional significance of cell volume regulatory mechanisms. Physiol Rev. 1998;78:247–306. [PubMed: 9457175]

7. Ablove RH, Babikian G, Moy OJ, Stegemann PM. Elevation in compartment pressure following hypovolemic shock and fluid resuscitation: A canine model. Orthopedics. 2006;29:443–5. [PubMed: 16729746]

8. Balogh Z, McKinley BA, Cocanour CS, Kozar RA, Valdivia A, Sailors RM, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. Arch Surg. 2003;138:637–42. [PubMed: 12799335]

9. Boldt J, Ince C. The impact of fluid therapy on microcirculation and tissue oxygenation in hypovolemic patients: A review. Intensive Care Med. 2010;36:1299–308. [PubMed: 20502873]

10. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, et al. The coagulopathy of trauma: A review of mechanisms. J Trauma. 2008;65:748–54. [PubMed: 18849786]

11. Revell M, Greaves I, Porter K. Endpoints for fluid resuscitation in hemorrhagic shock. J Trauma. 2003;54:S63–7. [PubMed: 12768105]

12. Kreimeier U, Prueckner S, Peter K. Permissive hypotension. Schweiz Med Wochenschr. 2000;130:1516–24. [PubMed: 11092054]

13. Cherkas D. Traumatic hemorrhagic shock: Advances in fluid management. Emerg Med Pract. 2011;13:1–19. [PubMed: 22164397]

14. Shah KJ, Chiu WC, Scalea TM, Carlson DE. Detrimental effects of rapid fluid resuscitation on hepatocellular function and survival after hemorrhagic shock. Shock. 2002;18:242–7. [PubMed: 12353925]

15. Bickell WH, Wall MJ, Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331:1105–9. [PubMed: 7935634]

16. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: Impact on in-hospital mortality. J Trauma. 2002;52:1141–6. [PubMed: 12045644]

17. Sampalis JS, Tamim H, Denis R, Boukas S, Ruest SA, Nikolis A, et al. Ineffectiveness of on-site intravenous lines: Is prehospital time the culprit? J Trauma. 1997;43:608–15. [PubMed: 9356056]

18. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg. 1986;73:783–5. [PubMed: 3533203]

19. Kwan I, Bunn F, Roberts I. WHO Pre-Hospital Trauma Care Steering Committee. Timing and volume of fluid administration for patients with bleeding. Cochrane Database Syst Rev. 2003;3:CD002245. [PubMed: 12917926]

20. Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D. A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. Health Technol Assess. 2000;4:1–57. [PubMed: 11109030]

21. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, et al. Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: Preliminary results of a randomized controlled trial. J Trauma. 2011;70:652–63. [PubMed: 21610356]

22. Beekley AC. Damage control resuscitation: A sensible approach to the exsanguinating surgical patient. Crit Care Med. 2008;36:S267–74. [PubMed: 18594252]

23. Rangarajan K, Subramanian A, Pandey RM. Determinants of mortality in trauma patients following massive blood transfusion. J Emerg Trauma Shock. 2011;4:58–63. [PMCID: PMC3097582] [PubMed: 21633570]

24. Hannon T. Trauma blood management: Avoiding the collateral damage of trauma resuscitation protocols. Hematology Am Soc Hematol Educ Program 2010. 2010:463–4. [PubMed: 21239836]

25. Jansen JO, Thomas R, Loudon MA, Brooks A. Damage control resuscitation for patients with major trauma. BMJ. 2009;338:b1778. [PubMed: 19502278]

26. Martin RS, Kilgo PD, Miller PR, Hoth JJ, Meredith JW, Chang MC. Injury-associated hypothermia: An analysis of the 2004 national trauma data bank. Shock. 2005;24:114–8. [PubMed: 16044080]

27. Asensio JA, McDuffie L, Petrone P, Roldan G, Forno W, Gambaro E, et al. Reliable variables in the exsanguinated patient which indicate damage control and predict outcome. Am J Surg. 2001;182:743–51. [PubMed: 11839351]

28. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, et al. Massive transfusion protocols: The role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg. 2009;209:198–205. [PubMed: 19632596]

29. CRASH-2 trial collaborators. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. Lancet. 2010;376:23–32. [PubMed: 20554319]

30. Hirshberg A, Sheffer N, Barnea O. Computer simulation of hypothermia during “damage control” laparotomy. World J Surg. 1999;23:960–5. [PubMed: 10449828]

31. Sagraves SG, Toschlog EA, Rotondo MF. Damage control surgery — The intensivist's role. J Intensive Care Med. 2006;21:5–16. [PubMed: 16698739]

32. Hsu JM, Pham TN. Damage control in the injured patient. Int J Crit Illn Inj Sci. 2011;1:66–72. [PMCID: PMC3209990] [PubMed: 22096776]

33. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, et al. Management of bleeding following major trauma: An updated European guideline. Crit Care. 2010;14:R52. [PMCID: PMC2887168] [PubMed: 20370902]

34. Tremblay LN, Rizoli SB, Brenneman FD. Advances in fluid resuscitation of hemorrhagic shock. Can J Surg. 2001;44:172–9. [PMCID: PMC3699117] [PubMed: 11407826]

35. Dutta R, Chaturvedi R. Fluid therapy in trauma. MAJFI. 2010;66:312–6. [PMCID: PMC4919829] [PubMed: 27365732]

36. Bouglé A, Harrois A, Duranteau J. Resuscitative strategies in traumatic hemorrhagic shock. Ann Intensive Care. 2013;3:1. [PMCID: PMC3626904] [PubMed: 23311726]

37. Boldt J. Volume replacement in the surgical patient — Does the type of solution make a difference? Br J Anaesth. 2000;84:783–93. [PubMed: 10895757]

38. Boldt J. Fluid choice for resuscitation of the trauma patient: A review of the physiological, pharmacological, and clinical evidence. Can J Anaesth. 2004;51:500–13. [PubMed: 15128639]

39. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev. 2013;2:CD000567. [PubMed: 23450531]

40. Shires GT, Browder LK, Steljes TP, Williams SJ, Browder TD, Barber AE. The effect of shock resuscitation fluids on apoptosis. Am J Surg. 2005;189:85–91. [PubMed: 15701499]

41. Alam HB, Sun L, Ruff P, Austin B, Burris D, Rhee P. E- and P-selectin expression depends on the resuscitation fluid used in hemorrhaged rats. J Surg Res. 2000;94:145–52. [PubMed: 11104654]

42. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: Systematic review of randomised controlled trials. BMJ. 1998;317:235–40. [PMCID: PMC28613] [PubMed: 9677209]

43. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, George Institute for International Health. Myburgh J, Cooper DJ, et al., editors. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med. 2007;357:874–84. [PubMed: 17761591]

Figures and Tables

Table 1

Adapted from management of hypovolemic shock in trauma patient; NSW Institute of Trauma and Injury Management; January 2007 SH PN: (T1) 070034

The Management of Hypotension Shock in the Trauma Patient

⇩

If definitive care is not available in your facility make early contact with retrieval services

Primary Survey
Includes organising the trauma team, calling the surgeon and notifying the blood bank.
Also consider early call to Retrieval Services (AMRS "formally MRU")

⇩

Airway/C-spine	Breathing	Circulation	Disability	Exposure/ environment	Adjuncts
• Protect airway secure if unstable • Airway adjunct as needed • Control of C-spine	• Definitive control of airway • Oxygen	• Secure venous access × 2 large bore cannula • Blood ◦ X match ◦ FBC ◦ EUC's ◦ Creatinine ◦ ABG's ◦ Blood ETOH ◦ Control external bleeding	• Assess neurological status • AVPU ◦ Alert ◦ Resounds to vocal stimuli ◦ Respond to painful stimuli ◦ Unresponsive	• Undress patient • Maintain temperature	• X-ray ◦ Chest ◦ Pelvis ◦ Lateral C-spine

⇩

Remember – BP and HR will not identify all trauma patients who are in shock
Assess - History and perfusion Indices – ABG's, Base deficit, lactate, HB and HCT

⇩

Perform secondary survey ⇦ NO **SIGNS OF SHOCK?**

⇩ YES

Identify the source of haemorrhage				
External	Long bones	Chest	Abdomen	Retroperitoneum
☐ Careful visual inspection	☐ Careful visual inspection	◦ Chest X-ray	◦ DPA and/or fast	☐ Pelvic X-ray

⇩

* Diagnostic Peritoneal Aspiration (DPA). > 10ml of frank blood = positive DPA
** Focused abdominal Sonography in Trauma (FAST). Free Fluid = Positive Fast

Interventions				
External	Long bones	Chest	Abdomen	Retroperitoneum
☐ Careful visual inspection	☐ Splint +/− reduce#t	◦ Chest tube	◦ Emergency tLaprotomy	☐ Externally stabilise pelvis ☐ Emergency angiogram

In the presence of uncontrolled haemorrhage and a delay of greater than 30 minutes to operative haemostasis, infuse small aliquots (100-200 mls) of fluid to maintain systolic blood pressure between 80-90 mm Hg. Use caution in the elderly. Contraindicated in the unconscious patient without a palpable blood pressure. Maintain the systolic blood pressure >90 mm Hg for those with a traumatic brain injury

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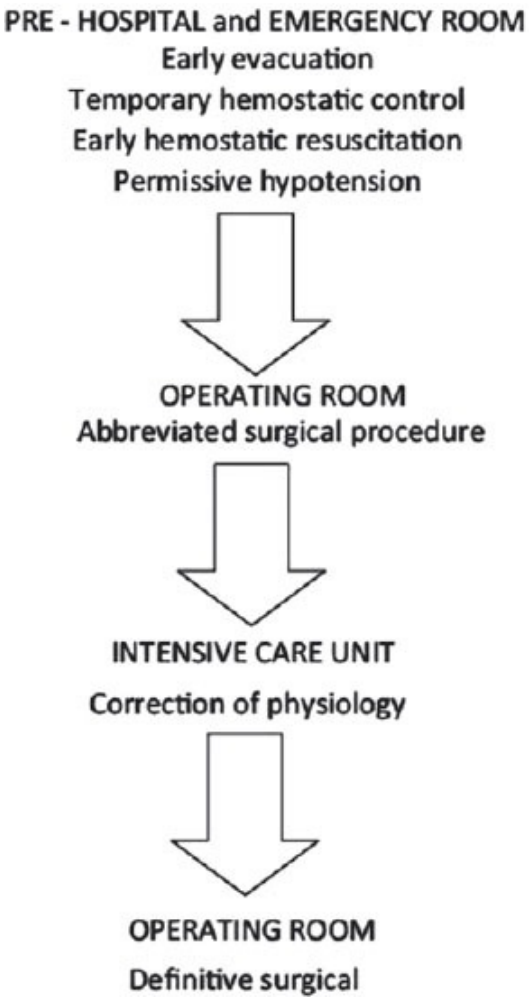
Table 2

Characteristics predictive of "exsanguinating syndrome" and indication of for damage contol from Asensio *et al.*

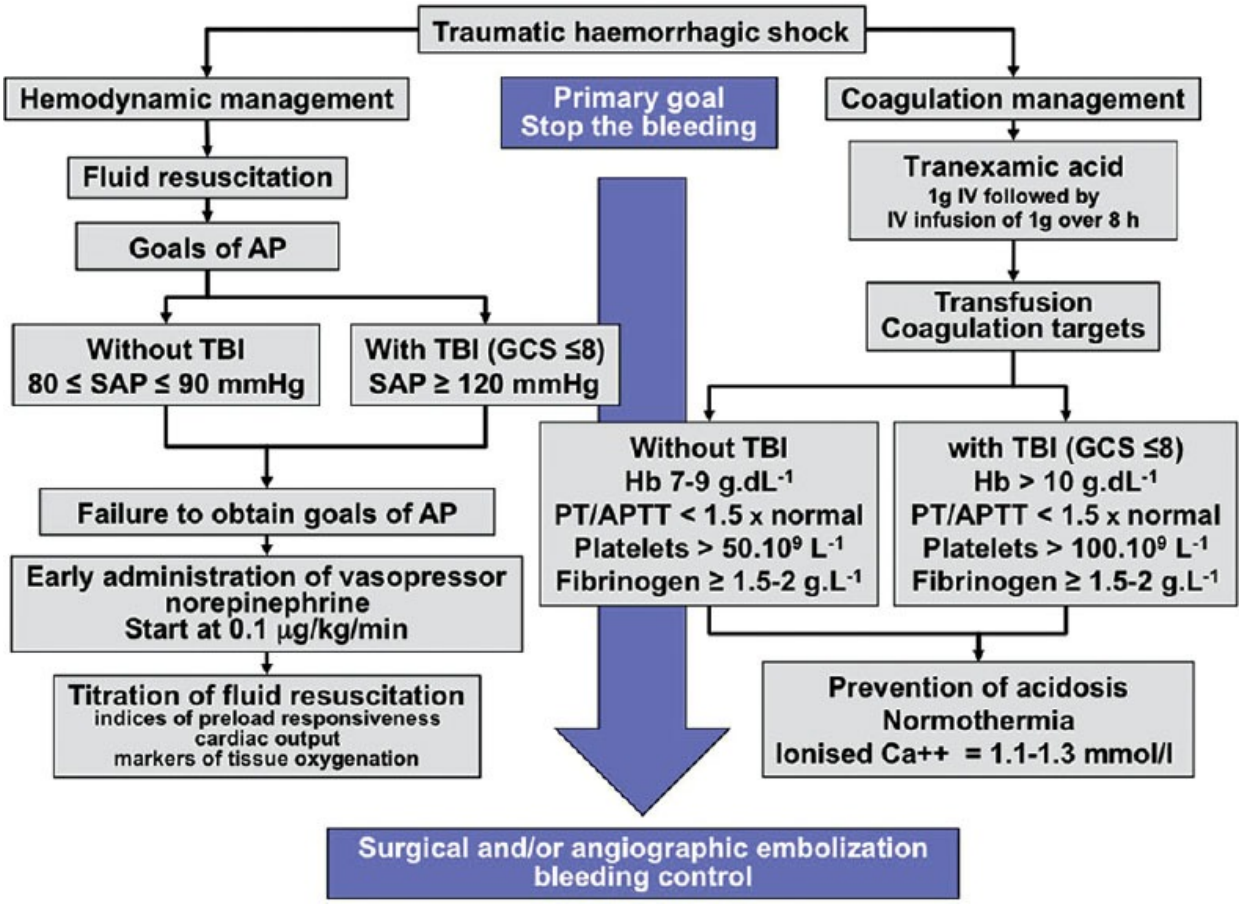
Revised trauma score ≤5
pH ≤7.2
Temperature ≤34°C
≥2000 ml crystalloid or ≥ units packed blood cells resuscitation in the emergency department
Multiple mass casualities
Multisystem trauma with major abdominal injury
Major abdominal injury
Open pelvic fracture with major abdominal injury
Major abdominal injury with need to evaluate early possible extra abdominal injury
Traumatic amputation of limb with major abdominal injury
Need for emergency department thoracotomy
Need for adjuctive use of angioembolization

Figure 1



Damage Control Sequence[31]

Figure 2



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Flow chart of initial management of traumatic hemorrhagic shock. In the acute phase of traumatic hemorrhagic shock, the therapeutic priority is to stop the bleeding. As long as this bleeding is not controlled, the physician must manage fluid resuscitation, vasopressors, and blood transfusion to prevent or treat acute coagulopathy of trauma (AP = Arterial pressure, SAP = Systolic arterial pressure, TBI = Trauma brain injury, Hb = Hemoglobin, PT = Prothrombin time, APTT = Activated partial thromboplastin time)[36]

Table 3

Resuscitation fluids

Fluid	Advantages	Disadvantages
Lactate ringer	Provides better buffer for metabolic acidosis	Increases endothelial dysfunction and neutrophil activation with increase in cellular damage[40]
Normal saline	Commonly used for resuscitation, no immunological effects	Causes hyperchloremic acidosis especially when given in large doses, increased incidence of dilutional coagulopathy[41]
Human serum albumin	Decreased volume required as compared to crystalloids	1.68 fold increase in relative risk of death as compared to crystalloids[42] Leakage to extra vascular spaces leads to worsening of edema Increased mortality for patients with TBI who were resuscitated with 4% albumin (SAFE trail — 2007 sub group analysis)[43]
Hypertonic saline	Volume expansion and positive immunological effects; especially used in TBI for raised intracranial tension (ICP)[13]	Concerns regarding hypernatremia and hyperchloremia exists[13]
Hypertonic saline with dextran	Increases cerebral perfusion in head injury with hemorrhagic shock, decrease ICP[13]	Posttrauma attenuation of multi organ dysfunction[13]
Blood transfusion	Reduces the requirement of cyrstalloids	Needs cross matching, usually not available immediately, usual transfusion related complication

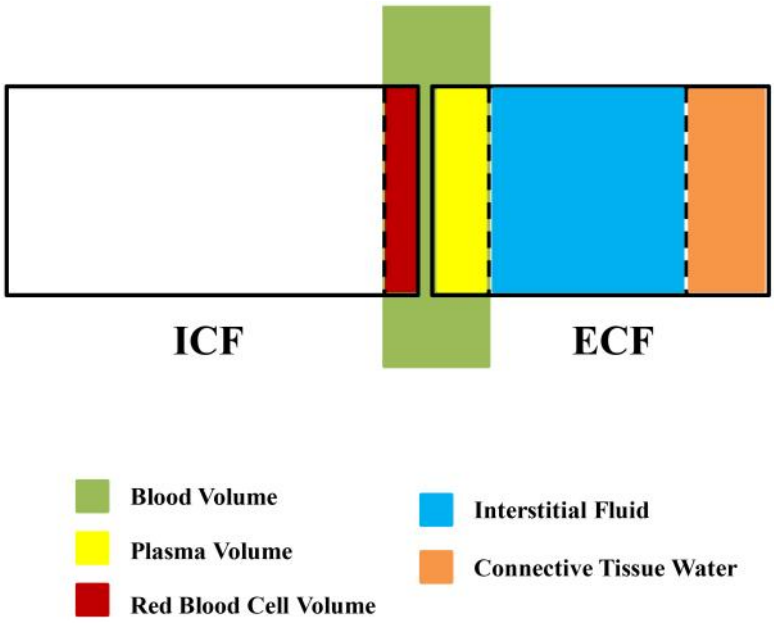
TBI = Traumatic brain injury, ICP = Intracranial pressure

FLUIDS AND ELECTROLYTES

Epidemiology/Pathophysiology

In an otherwise healthy individual, daily volume requirement estimations may be derived from calculations of weight (30-40ml/kg/day), body surface area (1.5L/meter2/day), and metabolic rate (100ml/100kcal). However, these methods may be inaccurate in particular patients (ex: a sedentary obese patient, a frail elderly patient, a patient with cancer). Further, surgical conditions such as trauma, acute peritonitis or abscess can result in acute volume loss, inadequate intake and altered metabolic requirements that must be considered when designing a treatment strategy.

A patient's homeostasis is related to total body water and its distribution between intra and extracellular spaces. Electrolytes are distributed throughout the system and held in various concentrations dependent upon gradients created by active and permissive transport across cell membranes. Up to 60% of the patient's weight is comprised of water that is distributed between intracellular and extracellular fluid compartments and is dependent upon solute concentrations, osmolarity and the semi-permeable cellular membranes.



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4096820/figure/F1/

Volume status is a term that directly relates to the extracellular space. This is comprised of intravascular ('blood': cell + plasma) and interstitial volume. Common causes of intracellular electrolyte and volume loss are directly related to extracellular causes.

Table 2: Causes of Intravascular Volume Loss
Hemorrhagic hypovolemia
Chest: Aortic disruption, pulmonary parenchyma trauma, pulmonary/intercostals vascular injury, hemoptysis
Abdomen/pelvis/retroperitoneum: GI hemorrhage (esophageal varices, ulcers, vascular anomalies), solid-organ injuries (liver, spleen, kidney), vascular (trauma, aneurysmal rupture)
Gynecologic disorders: ruptured ectopic pregnancy, peripartum hemorrhage, abnormal uterine bleeding, ovarian cyst rupture, etc
Orthopedic: Large bone fractures, pelvic fracture, multiple fractures
Extremity and skin surfaces
Major vascular injuries
Large soft tissue injuries
Nonhemorrhagic hypovolemia
GI disorders: vomiting, diarrhea, ascites
Burns
Environmental exposure or neglect
Renal salt wasting

Source: http://img.medscapestatic.com/pi/meds/ckb/33/26533.jpg

As the access to the system is either through the GI tract (oral intake) or via intravenous administration, treating the extracellular space is key to accessing and managing the intracellular space. Although the term resuscitation is commonly used to describe an immediate intervention to restore circulating intravascular volume and cardiac output, the ultimate goal is the restoration of cellular perfusion and correction of electrolyte and metabolic disarray.

In the presence of disease, estimations of fluid requirements become less reliable and fluid/electrolyte administration must relate closely to clinical context (ex: hemorrhage, emesis, diarrhea, oliguria with acute renal failure, third spacing of fluid in CHF or cirrhosis). An understanding of the patient's underlying medical conditions (ex: congestive heart failure, renal insufficiency, diabetes mellitus) and how they might contribute to the pathophysiological state ensures that the clinician applies proper goal-directed fluid and electrolyte therapy, maximize cardiovascular sufficiency, and restoration of cellular respiration.

Resuscitation versus Maintenance Volume Administration

Volume resuscitation implies restoration of cardiac output through the use of intravenous solutions with an osmolarity that will allow it to remain within the circulating volume and not be lost quickly into the intracellular or interstitial space. Maintenance fluids take into consideration the daily needs of the entire system for normal homeostatic function in order to maintain a euvolemic state.

Determination of the need for intravenous volume administration is considered with each clinical context and objective data. For example, a patient with a large scalp laceration, concurrent tachycardia, hypotension, tachypnea and cool extremities with diminished pulses is exhibiting signs and symptoms of acute volume depletion from hemorrhage. Providing maintenance volume will not restore adequate vascular volume quickly enough to establish normal cardiac output and avoid progressive hypoxia and metabolic acidosis. Once adequate vascular volume expansion and treatment of the anemia/coagulopathy has taken place, restoration of

maintenance fluid needs can be determined and provided in order to maintain stabilization, until the patient is capable of adequate oral intake. Proper monitoring such as trends of the patient's vital signs and urine output can assist with determining whether or not the initial maintenance fluid calculations are adequate or additional resuscitative vascular volume expansion may be required.

Endogenous Factors that Affect Renal Control of Sodium and Water Excretion

Fluid requirements begin with the understanding of losses incurred from normal homeostasis (obligatory water loss). In an average adult, this comes from insensible sources (exhalation, sweat), feces and urine. External sources of volume come from oral fluids, food and IV infusion. Internal sources include metabolic water production from oxidation of food (Krebs cycle).

Urine output is required to remove metabolic byproducts and ingested excess solute. This volume is dependent in part upon the daily solute excretory load and the kidney's ability to concentrate urine. If urine volume is less than this amount, solutes will accumulate and renal failure will evolve. Alternatively, water ingestion beyond that required for homeostasis will be excreted. Thus water and electrolyte balance requires adequate renal filtration, urinary concentration and excretion capability.

In the presence of adequate intake, volume regulation is predominantly exerted by renal function - water and electrolyte compositions are maintained by ingestion of more salt and water than is needed, and by the renal capacity to excrete the excess.

Volume status is regulated through the monitoring of systemic solute per unit volume, or osmolarity. Sodium, the most prominent electrolyte 'solute' in extracellular fluid, is used to monitor extracellular osmolarity. A disproportionate loss of water relative to sodium results in a concentrating osmolar effect. The system will need to conserve/retain water relative to sodium. Alternatively, if losses of extracellular volume are proportionate, for example, whole blood loss during surgery, the system will need to conserve both sodium and water in order to maintain normal osmolarity.

Water balance in the presence of sodium concentration, or hyperosmolarity, is controlled by hypothalamic antidiuretic hormone (ADH) and thirst response. Hyperosmolality and volume depletion are sensed in part by baroreceptors in the carotids, aorta and heart and contribute ADH secretion. Thirst response contributes by altering water intake. ADH stimulates water reabsorption from the nephron's distal collecting duct.

Dilution of the extracellular space is prevented in part by regulating sodium concentration. The adrenal hormone Aldosterone stimulates distal renal tubular cells to absorb sodium; in exchange potassium and hydrogen are excreted. Aldosterone effects do not concentrate urine directly, because it exchanges one ion for another. However, the system is foremost attempting to conserve and maintain volume by monitoring its extracellular osmolarity; adjustments in water and sodium reabsorption are performed towards this goal with the balance shifting depending upon the volume's concentration.

For example, in dehydration with hyperosmolarity, the balance between ADH stimulation and water reabsorption is greater than the production and effect of aldosterone. The result will be a return to normal osmolarity by returning water back to the system and allowing sodium to be

excreted (lower urine volume, higher concentration). In conditions of volume overload and hypo-osmolar state, aldosterone is created to increase sodium conservation, ADH is suppressed (urine volume increased and becomes dilute) and osmolarity is returned to baseline.

Cardiac output and blood pressure play a role in volume regulation. As above all else, the body must preserve the central nervous system and cardiac perfusion at all cost, the sympathetic nervous system will commence shunting blood away from the remaining organ systems and the periphery to preserve flow to these central organs. The result will be a reduction in kidney perfusion and with it reduced glomerular filtration.

Glomerular blood flow and filtration is sensed by the arterial juxtaglomerular apparatus resulting in either suppression (adequate or high GFR) or stimulation (low GFR) of these cells to produce renin.

With hypovolemia (ex: blood loss, volume depletion), reduced GFR will be sensed by the kidney's juxtaglomerular cells in the afferent and efferent arterioles resulting in renin production and stimulation of renin-angiotensin cascade.

In this case, the body is trying to conserve volume. Hence not only has vasopressin been stimulated though central arterial pressure loss and osmolar shifts but aldosterone is also called upon to assist with sodium retention to maintain sodium concentrations and iso-osmolarity. The result will be a low urine volume, but its osmolarity may not be as high as with hyperosmolar dehydration (ex: dehydration from sweating or fever, volume depletion from emesis, diarrhea) because both ADH and aldosterone are working in balance here rather than ADH greater than aldosterone.

In conditions where excessive amounts of volume and electrolytes are lost (ex: enterocutaneous fistula) renal function may be effected by secondary hyperaldosteronism provoked by sodium loss through the fistula. Urinary sodium can be monitored. A concentration below 20 mM suggests inadequate sodium replacement, and this is certain when the level falls below 10 mM. Thus it is important to monitor fistula output and replace the losses with a solution containing adequate amounts of sodium.

With hypervolemia and sodium overload, glomerular flow is adequate, suppressing renin-angiotensin cascade and aldosterone production, allowing excretion of sodium. When a positive free water balance lowers the serum sodium concentration (ex: <135 mMol/L), cell volume receptors in the hypothalamus inhibit the secretion of ADH. Free water is excreted and circulating sodium is returned to normal levels. Atrial natriuretic factor (ANF) hormone is released by cardiac myocytes in response to elevated blood volume. Its effect counters that of renin-angiotensin-aldosterone and promotes natriuresis by promoting glomerular filtration and reducing distal tubular sodium reabsorption.

An important distinction must be made between dehydration and volume depletion, as the terms are mistakenly used interchangeably. Dehydration refers to a loss of total body water that can produce overall hypertonicity. Alternatively, volume depletion occurs when there is a loss of extracellular fluid volume. While both conditions can occur simultaneously, the management, including the rate and type of fluids used may differ. Resuscitation with restoration of the extracellular space's intravascular volume is a priority, though once this has been re-established, focus must shift to address intracellular needs.

SIGNS AND SYMPTOMS

Symptoms, Signs and Physical Findings of Volume Depletion and Dehydration

As with other information, the objective data must be taken in the context of the patient's presentation and relevant medical history. Patients may complain of thirst, nausea, emesis or stool output at rates greater than volume input. Lethargy, confusion and obtundation may occur. Vital signs are an important diagnostic clue, especially if the patient's values when (s)he was previously well are available for comparison. Similar to laboratory values, trends over time are more helpful than singular, random numbers. Progressive tachycardia, clinical orthostasis, postural hypotension, narrowed pulse pressure are helpful clues. Tachypnea may occur from volume loss and resultant metabolic acidosis. Additional physical examination findings that suggest intracellular in addition to extracellular/vascular volume loss may include dry mucous membranes, reduced skin/tongue turgor, and prolonged capillary refill (most effective in infants/children). Muscle weakness can occur from potassium, magnesium and calcium electrolyte disarray. Patients may have reduced urine output (< 0.5cc/kg/hr), commonly with a change in urine color and concentration. Oliguria may be an initial finding in acute kidney injury (AKI) whose etiology is commonly related to pre-renal etiologies including volume depletion.

Relevant Diagnostic Studies

Metabolic Panel
Basic: Serum Sodium, Potassium, Chloride, Bicarbonate and Glucose; Blood Urea Nitrogen and Creatinine

Complete: includes Magnesium, Calcium, Total Protein, Albumin, Globulin, Total Bilirubin, Alkaline Phosphatase, AST, ALT, Glomerular Filtration Rate (GFR)

Serum Lactate

Complete Blood Count: Hematocrit

Urinalysis: Specific Gravity, Ketones, Protein, Sodium, Osmotic Concentration (Osmolarity)

PEARLS

Chloride will be low with gastric fluid loss (emesis, NG Tube aspiration, pyloric stenosis) leading to hypochloremic hypokalemic metabolic alkalosis with paradoxical aciduria.
Poor tissue perfusion in volume depletion and dehydration results in lactic acidosis.
Bicarbonate is reduced in metabolic acidosis (ex: lactic, diabetic ketoacidosis [DKA])
Bicarbonate may also be lost in diarrheal stool output (non anion gap acidosis).
Glucose may be high from DKA or hyperosmolar hyperglycemic nonketotic coma (HONK)

BUN and creatinine levels may be elevated (BUN/Cr ratio > 20:1 suggests volume depletion pre-renal hypoperfusion)
Hemoconcentration in severe dehydration may lead to Hematocrit and albumin elevation, whereas rapid acute volume loss from hemorrhage may not change initial hematocrit or albumin levels.

Serum Osmolarity (nl 275–295 mosm/kg) is elevated in dehydration, hyperglycemia (DKA, HONK), Diabetes Insipidus
Serum Osmolarity is decreased in SIADH, Hyponatremia (CHF, Cirrhosis)
Oliguria may suggest significant volume depletion and/or dehydration
Urine Specific Gravity may be elevated in volume depletion and dehydration (an exception: Diabetes Insipidus)
Ketonuria may be present in dehydration
Urine Sodium may be low (< 20meg/L) in volume depletion (aldosteroma)
Urine chloride may be low in metabolic alkalosis (emesis)
Consider electrolyte analysis of fluid from drains to assist with replacement fluid needs (ex: pancreatic or biliary drain, gastric fluid)
Urine Osmolarity may be elevated (> 400mosm/kg) in volume depletion and dehydration

Serum Electrolytes: Normal Ranges for use with Management Needs Assessment

Electrolyte	Ref Range & Units
SODIUM	135 - 145 mmol/L
POTASSIUM	3.4 - 5.0 mmol/L
CHLORIDE	98 - 108 mmol/L
CO2	23 - 32 mmol/L
BUN	8 - 25 mg/dL
CREATININE	0.60 - 1.50 mg/dL
GLUCOSE	70 - 110 mg/dL
CALCIUM	8.5 - 10.5 mg/dL
EGFR	>60 mL/min/1.73m2
ANION GAP	3 - 17 mmol/L
WHOLE BLOOD GLUCOSE	70 - 110 mg/dL
Calculated Osmolarity	200-300 mOsm/L

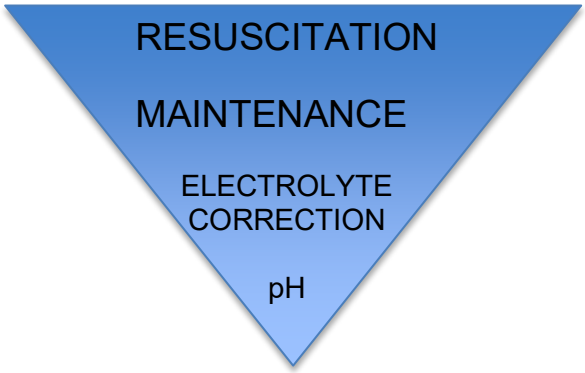
2 [Na(mEq/L) + 2 [K(mEq/L)] + [Glucose (mEq/dL)]/18 + [BUN (mEq/dL)]/2.8

It is important to review the treating institution's normal values. Analysis of a patient's basic metabolic panel should be done in the context of the patient's presentation. Previous known values are equally important to assist with establishing trends. Anticipating potential evolving metabolic derangements is helpful in designing treatment and management plans to reduce or avoid their occurrence (ex: nasogastric tube drainage, ileostomy output). If resuscitation is underway, the provider will be expected to adjust focus on maintenance of volume and metabolic/electrolyte correction as needed with restoration of cardiovascular sufficiency.

Management

Regardless of the etiology of volume depletion, the mainstay of treatment strategy is a goal-directed resuscitation to restore intravascular volume. This will contribute to improved cardiovascular function and tissue perfusion. As the extracellular space is restored, focus can begin to shift towards maintaining the current extracellular volume state and restoring intracellular volume. Electrolyte disarray may be anticipated from the clinical context and

verified using diagnostic tests. Correction can occur during and after the maintenance phase is established. With adequate tissue perfusion, most pH abnormalities should correct without the need for exogenous buffer. The inverted pyramid below illustrates the focus of acute management in descending order of priority:



Measuring Fluid Balance

There are several tools available to monitor patients' intravascular resuscitation. The clinical context is always very helpful in anticipating potential volume and metabolic derangements and in creating a management strategy. Monitoring for changes in vital signs, including the development of fever, is used to determine resuscitation as well as adjusting for needs. Trend analysis of laboratory values such as serum and urine electrolytes and osmolarity, BUN, creatinine and GFR can be used to tailor specific needs. Requesting staff assistance with 'Strict Inputs & Outputs' on patients by accurately measuring each source of input (ex: IV fluid and medication volumes, oral intake calculations) and output sources (urine, stool/ostomy [emesis/diarrhea volume], and drains [ex: NGT, JP, chest tube]). These will assist with identification of input adjustment needs relative to calculated output measured. These can be trended and re-calculated with each shift.

Sources of Fluid Loss or Gain may include:

Loss
- Hemorrhage
- Emesis
- Stool/ostomy output
- Drains
- Diuresis

Gain
- Excessive IV fluids
- Excessive sodium intake
- Reduced Inotropy (ex: CHF)
- Renal Parenchymal Disease
- Cirrhosis

Physical Findings suggestive of Volume Depletion/Dehydration or Fluid Overload:

Finding	Volume Depletion/Dehydration	Overload
Body Weight	Loss	Gain
Pulse Pressure	Wide (early) Narrow (Late)	Wide
Integument	Dry, Low Turgor	Pitting Edema
Mucous Membranes	Dry	Moist

Compare and Contrast Various Resuscitation Strategies for Patients who are Volume Depleted or in Hemorrhagic Shock

Initial management of Volume Depletion includes restoration of intravascular circulating volume. 20cc/kg boluses of isotonic crystalloid (ex: 0.9%NS, LR) can be instituted. Lactated Ringer's solution is the fluid of choice for large volume resuscitation, i.e. trauma patients. Goals of treatment include improvement of vital signs and establishment of urine output.
Acute hemorrhage: Given a clinical context (ex: blunt, penetrating trauma, acute GI bleeding, leaking aortic aneurysm),in-hospital resuscitation discussion including the use of crystalloid versus Type O Rh -, type-specific and cross-matched packed red blood cells followed by infusion ratio of packed RBCs, Fresh Frozen Plasma and Platelets in transfusion resuscitation and massive transfusion protocols.

Once resuscitation is successful, focus can shift towards maintenance of extravascular volume, resuscitation of intracellular volume, and correction of metabolic disarray.

Electrolyte Composition of the Following Solutions

Normal Saline (0.9%NaCl)
Ringer's Lactate (Balanced Solution, Hartmann's Solution)
1/2 Normal Saline (0.45%NaCl)
5% dextrose in water (D5W)

Solution	pH	Na^+	Cl^-	K^+	Ca^{++}	Lactate	Glucose	Osmolality
.9% Normal Saline	5.0	154	154	0	0	0	0	308
Lactated Ringers	6.5	130	109	4	3	28	0	275
5% Dextrose in Water (D_5W)	4.0	0	0	0	0	0	50 g/L	252
.45% Normal Saline with Dextrose ($D_5$1/2 NS)	4.5	77	77	0	0	0	50 g/L	406
0.45% Normal Saline (1/2 NS)	5.0	77	77	0	0	0	0	155

Source: http://www.medscape.org/viewarticle/503138

Hypertonic solution has an osmolarity greater than 340mOsm/kg; Isotonic solutions have an osmolarity between 240-340mOsm/kg; Hypotonic solutions have an osmolarity less than 250mOsm/kg. Hypertonic and isotonic solutions are considered for resuscitation. Isotonic and hypotonic solutions may be chosen for maintenance and electrolyte correction.

POSTOPERATIVE CARE

Specific Problems

Patients must be monitored closely with frequent vital sign checks for evolving tachycardia and pulse pressure shifts from volume output exceeding input. Continued measurements of intake versus output are required. Maintenance fluid therapy may require supplemental resuscitation when output exceeds input. Resuscitation may be provided in the form of bolus isotonic solutions (ex: 10-20cc/kg) followed by maintenance infusion. Losses from drains (ex: NG tube,

biliary drains) are replaced ml for ml with solutions whose electrolyte composition closely mirrors that of the fluid lost. For example, nasogastric aspirate may be replaced using NaCl; peripancreatic fluid loss may be replaced ml for ml using Lactated Ringers solution. This administration is added to, not in replacement for the maintenance infusion.

In the following situations, serum Na, K, HCO3, Cl will remain stable (0), rise considerably (++), rise moderately (+), fall moderately (-), or fall considerably (--):
Excessive Gastric Losses
High Volume Pancreatic Fistula
Small Intestinal Fistula
Biliary Fistula
Diarrhea

Excessive Gastric Losses (Eventual Chloride-Responsive Metabolic Alkalosis)

Na	K	HCO3	Cl
Fall ++	Fall +	Rise	Fall ++

High Volume Pancreatic Fistula (Hyponatremic Hypokalemic Metabolic Acidosis)

Na	K	HCO3	Cl
Fall ++	Fall +	Fall ++	Stable

Small Intestine Fistula (Hyponatremic Hypokalemic Metabolic Acidosis)

Na	K	HCO3	Cl
Fall ++	Fall +	Fall ++	Fall +

Biliary Fistula

Na	K	HCO3	Cl
Fall +	Fall +	Stable	Fall +

Diarrhea (Non-Anion Gap Hyperchloremic Metabolic Acidosis)

Na	K	HCO3	Cl
Rise	Fall ++	Fall ++	Rise

Sources of average daily fluid production/loss:
Salivary glands 1.5L
Gastric glands 1.5 L
Pancreas 1 L
Bile Production 1 L

Duodenal (ex: Brunner's glands) 200 mL
Jejunum + Ileum 1.5-2 L

Depending on the daily oral intake, 8 to 10 L of fluid passes through the jejunum each day, (more in the presence of inflammation, infection or obstruction).

98% of this fluid is normally absorbed most occurring proximal to the ileocecal valve (colon absorbs up to 2L); usually 100 to 200 mL of fluid is excreted in the stool.

Composition of the enteral/organ secretions at various levels of the gastrointestinal tract includes the following:

Gastric: H, Cl, Na, K,
Duodenal: H, Cl, Na, K
Bile: Na, Cl
Pancreas: Na, K, HCO3
Small Intestine: Na K Mg HCO3

In general, there is a potential for acute fluid loss and electrolyte imbalance with pancreatic or proximal intestinal fluid loss from conditions such as pancreatic or small intestinal fistulae. Water and electrolytes (especially sodium, magnesium and bicarbonate) inevitably accompany this fluid, as do essential nutrients.

In general, gastric losses from emesis and NG tube aspiration will contain higher concentrations of H, Na, K and Cl, resulting in a volume depletion and chloride-responsive metabolic alkalosis. Losses from peripancreatic, and intestinal pathologies below the pylorus such as EC fistulae and diarrhea will contain more K and bicarbonate anion resulting in a volume depletion and metabolic acidosis. Choice of IV resuscitation and maintenance fluids may be chosen in anticipation of such risk as well as to reflect these conditions that are verified by diagnostic serum electrolyte tests.

Normal ‘Fed’ versus ‘Fasting’ state and electrolyte variations
Electrolyte secretions differ significantly between the fasting and fed states. Feeding increases the H ion concentration from about 50 mM to up to 100 mM, increases Cl from 90 to 120 mM, but decreases sodium from 40 to about 25 mM. Na concentration of about 140 mM is independent of the activity state of the pancreas, but the HCO3 concentration increases from 40 to up to 145 mM following stimulation.

Fistulous discharge at the level of the upper jejunum is therefore associated with significant losses of sodium, chloride, and bicarbonate ions.

Fluid volumes can be replaced intravenously or orally. In general each liter of fluid lost from a stoma or fistula contains 100 mmol of sodium. Treatment must include isotonic solutions containing Na. This is replaced cc for cc collected from fistulae and stomas. In general, most patients will not be able to manage more than 1.5 to 2.0 L in 24 hours period. If greater volumes are required, IV support is needed.

In the following situations, indicate whether serum and urine Na, K, HCO3, Cl and osmolality will remain stable (0), rise considerably (++), rise moderately (+), fall moderately (-), or fall considerably (--):

Acute Tubular Necrosis
Dehydration
Inappropriate ADH secretion (SIADH)
Diabetes Insipidus
Congestive Heart Failure

ATN (ex: Nephrotoxic)

Na	U Na	K	HCO3	Cl	Osm
Fall	Rise	Rise or Fall	Fall	Fall	Rise

Dehydration (Determine Etiology ex: Emesis, Diarrhea, Sweating + Poor PO Intake)

Na	U Na	K	HCO3	Cl	Osm
Rise or Fall	Fall	Rise or Fall	Rise or Fall	Rise or Fall	Rise

SIADH

Na	U Na	K	HCO3	Cl	Osm
Fall	Rise	Stable	Stable	Stable	Fall (< U.Osm)

DI

Na	U Na	K	HCO3	Cl	Osm
Rise	Fall	Rise	Stable	Rise	Rise

CHF (reduced GFR, elevated renin-angiotensin-aldosterone, vasopressin [ADH])

Na	U Na	K	HCO3	Cl	Osm
Stable/Fall	Fall	Fall	Rise	Fall	Fall

Describe the possible causes, signs and symptoms, appropriate laboratory studies needed, and treatment of the following conditions:

Hypernatremia
Hyponatremia
Hyperkalemia
Hypokalemia
Hypomagnesemia
Hyperchloremia
Hypochloremia

HYPERNATREMIA

Causes:
Electrolytes are ingested and retained without corresponding amounts of water or when water is lost at a rate greater than the electrolytes.
Normally excess salt intake results in thirst response (increasing water intake) and ADH release

(reducing water loss).
Hypotonic fluid losses (ex: vomitus, infectious or cathartic induced diarrhea, glycosuria, osmotic or loop diuretic use, Diabetes Insipidus)
Hypothalamic atrophy or disease can reduce thirst response, (elderly), and aberrant ADH release (Diabetes Insipidus).

Normal range serum osmolality: 275-295 mosmol/L.
If both hypothalamic and renal function are intact, a rise in the serum sodium concentration (ex: 150meq/L) should result in plasma osmolality > 295mosmol/kg. This should normally cause ADH secretion to maximally concentration urine (> 600mosmol/kg). Exogenous ADH should not produce a further rise in the urine osmolality.

Diabetes Insipidus:
Urine osmolality is less than the plasma osmolality (< 300 mosmol/kg), consider central or nephrogenic diabetes insipidus. Exogenous ADH should result in reduced urine output and increased urine osmolarity.
Lab Tests: Basic metabolic panel, including glucose, creatinine; serum and urine osmolarity, urine Na

Intermediate urine osmolality (300 - 600 mosmol/kg), consider an osmotic diuresis or diabetes insipidus. ADH effect is maximal in hypernatremia from osmotic diuresis. Thus exogenous ADH will have no effect.

High urine osmolarity (> 600 mosmol/kg) is most likely due to extrarenal water losses in a dehydrated patient. Urine osmolality > 600 mosmol/kg, indicates secretion of and response to ADH. The treatment includes resuscitation of intravascular volume followed by isotonic or hypotonic solutions.

A volume depleted patient with high plasma osmolality and a low urine osmolality, consider diabetes insipidus.

Significant volume depletion (ex: emesis, diarrhea) will likely result in urine sodium < 25meq/L (aldosterone, sodium reabsorption).

Urine sodium > 100meq/L with normal renal function suggests excessive salt ingestion relative to free water (ex: 3%NaCl).

Calculations: What is the Free Water Deficit that must be infused to treat Hypernatremia?

$$\text{Water deficit} = \text{current TBW} \times \frac{\text{Serum Na}}{140} - 1$$

TBW (total body water) = approx 50% lean body weight
Ex: 75yo female 60kg with a serum Na 160
Water deficit = 0.50 X 60 ([160/140] – 1) = 4.3 liters
NB: does not include estimated losses from sweat, isosmotic loss in diarrhea or osmotic diuresis
Acute or Chronic Hypernatremia:

> Acute: deficit replaced in 24 hours; hourly infusion rate should exceed the water deficit divided by 24: Hourly infusion rate (mL/hour) > Water deficit in mL ÷ 24 hours; for patient above, 4300ml ÷ 24 = 180ml/hr
> or
> D5W 3-6 ml/kg/hr; measure serum Na every 1-2 hours until 145meq.

D5W at 1ml/kg/hr until serum Na is 140meq
Chronic: a fraction of the water deficit is replaced in 24 hours (i.e., enough water to lower the serum sodium by 10meq/L)
Desired water replacement in the first day in mL = 3 mL/kg body weight x 10
180ml X 10 = 1800ml/24hr
or
1.35ml/hr X pt.'s wt. (kg) – goal is approx. 10eq/l/24hours; measure serum Na every 6 hours

HYPONATREMIA

Elevated ADH: Volume Depletion, CHF, Cirrhosis, SIADH, Thiazide Diuretics, Adrenal Insufficiency
Low ADH: Chronic kidney disease, water intoxication (primary/psychogenic polydipsia)
Elevated Osmolarity: Hyperglycemia, Alcohol Ingestion
Normal Osmolarity: Elevated triglycerides, lipoproteins (jaundice), myeloma, mannitol

Lab Tests: Basic metabolic panel, including glucose, creatinine; consider CBC, LFTs, calcium
Timing: Acute (<24hrs ex: marathoners hydrating with water) vs Chronic (> 48hrs)
Symptom Severity:
- Mild/Moderate: fatigue nausea confusion ataxia (serum Na 121-129)
- Severe: obtundation, seizure, coma (serum Na < 120)

Treatment Goal: Increase the serum sodium by 4 to 6 meq/L over 4-24 hours but not to exceed 8 meq/L in 24-hour period (danger of too rapid a correction is central pontine myelinolysis).
- Treat Underlying Disease
  - Volume Depletion: isotonic, hypertonic saline (suppressing nl. ADH release, promoting excess free water excretion)
  - Adrenal Insufficiency: glucocorticoids (directly suppressing ADH release)
  - Secondary SIADH: reduce/discontinue use of Desmopressin (DDAVP), SSRIs [fluoxetine, sertraline]

Solutions

Hypertonic (moderate/severe symptoms, serum Na < 121) isotonic (mild/moderate symptoms, serum Na > 121)
Hypertonic Saline (3%NaCl): 1 mL/kg body weight of 3 percent saline = 1 meq/L increase in serum Na (note: rough estimate; serum values must be checked regularly. Overcorrection can occur when
a) hypovolemia is corrected, removing ADH release and causing excess water excretion resulting in faster/higher serum Na levels.
b) SIADH – causes excretion of serum Na (normal aldosterone and atrial naturietic peptide function) with water retention, resulting in slower/lower serum Na levels

Isotonic saline (0.9%NaCl): Raises serum Na by 1meq/L for each liter infused. Consider in volume depletion states (emesis, diarrhea, diuretic use). This will reduce ADH release, and increase free water loss.

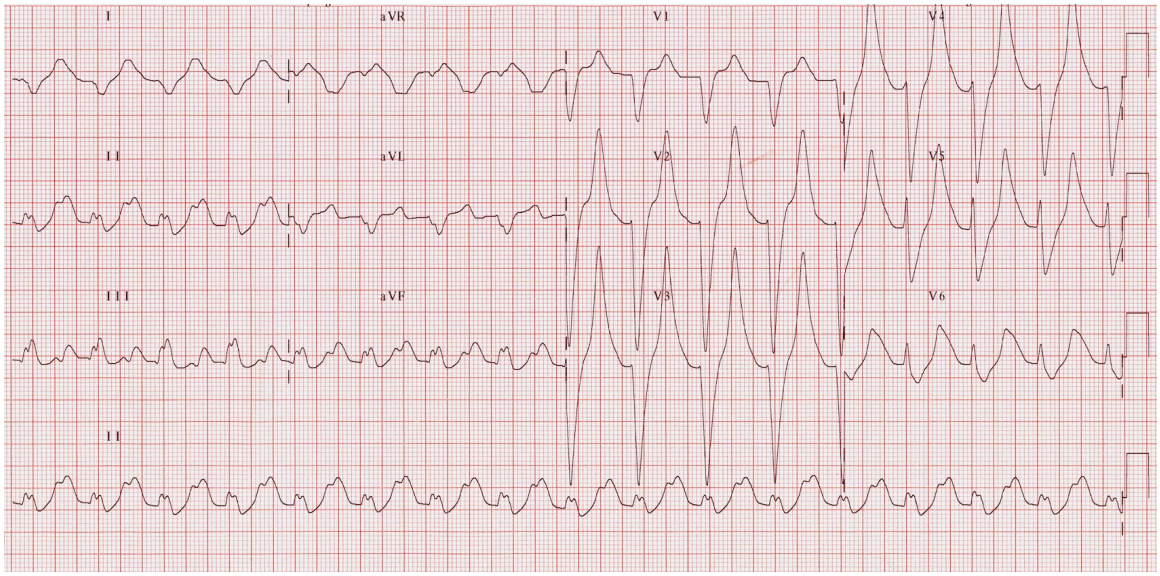
Volume restriction is preferred for edematous hyponatremic states (ex: CHF); isotonic saline may increase total body water with only minimum improvement in serum Na.

HYPERKALEMIA

Causes:
Renal dysfunction causing urinary K excretion (parenchymal disease; inhibition of renin-angiotensin-aldosterone [underlying disorder, drug-induced]).
Redistributive hyperkalemia most commonly occurs in uncontrolled hyperglycemia (e.g., diabetic ketoacidosis or hyperosmolar hyperglycemic state). Impaired insulin production or response, serum hyperosmolality shifts intracellular potassium into the ECF. Volume repletion and insulin will restore condition, though patients may still have whole body potassium deficit (ex: renin-aldosterone).

Lab Tests: Basic metabolic panel, including glucose, creatinine

Identification of EKG Abnormalities Consistent with Hyperkalemia (EPA-3)



Scenario: Patient with end-stage renal disease (ESRD) and missed dialysis; Crush injury; Hypertension treatment with ARB/ACE inhibitors, diuretic use such as spironolactone or amiloride; Transplant patient on tacrolimus or cyclosporine.

ECG: (Hyperkalemia)

(Source: http://cdn.lifeinthefastlane.com/wp-content/uploads/2011/02/ECG-Potassium-9.2.jpg)

ECG findings:
AV block
Prolonged PR interval
Peaked T waves
Widened QRS
Fusion of P and T wave into QRS

Hyperkalemia Treatment

Calcium chloride (central access) 500-1000mg (5-10cc of a 10% solution) infused over 2-3minutes (4.6meq elemental Ca in 10ml)

Calcium gluconate (peripheral access) 1000mg (10ml of a 10% solution) infused over 2-3 minutes (13.6 meq elemental Ca in 10ml)
(rapid onset of action)

Insulin (10 units regular) bolus injection with either D50 (50ml) or in 500ml D10W over 60 minutes
(onset action in 30-60 minutes)

Glucose may be held if serum level ≥250

Albuterol 10-20mg in 5ml saline nebulization (4X greater than usual bronchodilation dose); increases skeletal muscle Na-K-ATPase pump
(onset action variable)
Cation exchange resins (e.g., sodium polystyrene sulfonate, 15-30g) are indicated:
Potentially life-threatening hyperkalemia
Dialysis is not readily available
Other therapies to remove potassium (e.g., diuretics, rapid restoration of kidney function) have failed or are not possible
(onset action in hours)
Contraindications:
Postoperative patients
Patients with an ileus, small or large bowel obstruction or receiving opiates

Repeated doses of insulin and glucose is preferred in such patients until dialysis is available

Dialysis hyperkalemia is severe and expected to increase rapidly

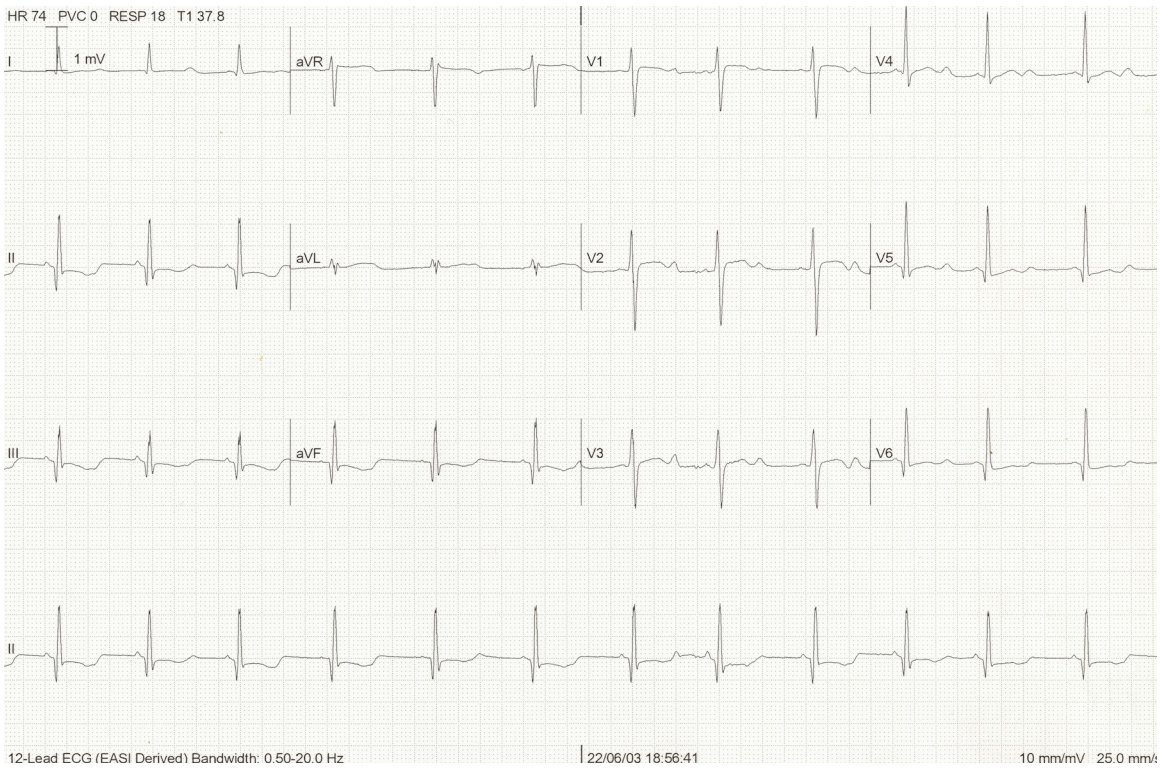
HYPOKALEMIA

Causes:
GI losses (diarrhea, vomiting)
Renal (diuretics, renal artery stenosis)

Tests: Basic metabolic panel, including glucose, creatinine, Mg, urine K, ECG (U wave)

Urine K < 20meq/L in volume depletion from diarrhea, insulin use,
Urine K > 40meq/L with diuretic use, vomiting, mineralocorticoid excess, Bartter and Gitelman syndromes (autosomal recessive renal disorders causing hypokalemic metabolic alkalosis)

Identification of EKG Abnormalities Consistent with Hypokalemia (EPA-3)



Scenario: Patient with enteritis, diarrhea and vomiting; diabetic ketoacidosis (as the pH improves with therapy, the serum K may fall precipitously); diuretic use (thiazides, furosemide); primary hyperaldosteronism

ECG (Hypokalemia)

(Source: http://cdn.lifeinthefastlane.com/wpcontent/uploads/2011/02/hypokalaemia2.jpg)

ECG findings:
Tachyarrhythmias
T wave inversion
ST depression
U waves
Prolonged QU interval

Hypokalemia Treatment
For every 1 mEq/L decrease in serum potassium, the potassium deficit is approximately 200-400 mEq.
Note that potassium values are difficult to correct when magnesium level is also low; both may need to be corrected.
Oral replacement when possible; most efficient, especially when larger doses are required more quickly.

Consider providing supplements with serum potassium levels < 3.8 mEq/L.

1-3 meq/kg/day in 2 - 4 divided doses to a maximum of 120 mEq over 6 hours; titrate to desired level – wait at least 1 hour after administration before checking serum K values

Note that KDur™ should be avoided when values need to be corrected quickly.

IV Treatment:
Peripheral IV
Maximum concentration through a peripheral line is 10 mEq/100 ml.
Minibag therapy: maximum of 20 mEq.
maximum infusion rate is 10 mEq per hour.

Central IV
20 mEq/100 ml is standard; maximum concentration of 20 mEq/50 ml for fluid restricted patients
Minibag therapy: maximum of 20 mEq.
Maximum infusion rate via central line is 20 mEq/hr with cardiac monitoring
Recommended to wait at least 1 hour after administration before checking serum K values

Oral + IV administration: maximum IV + PO of 120 mEq over 6 hour period with serum checks.

HYPOMAGNESEMIA

Causes:
Starvation
Alcohol dependence
Pancreatitis
Vomiting and nasogastric suction
Diarrhea
Ostomy and fistula output
Diuretics - Loop diuretics, osmotic diuretics, and long-term use of thiazides

Diagnostic Tests: Serum Mg, Total Protein, Serum K, Ca and Phos levels

Extracellular magnesium is protein bound; poor protein values may be a contributor.
Majority of Mg is reabsorbed in the kidney's ascending limb, and a lesser extent the PCT, thus diuretics may contribute to low Mg.

Hypomagnesemia may lead to hypokalemia; thus treating magnesium levels are important while supplementing potassium.

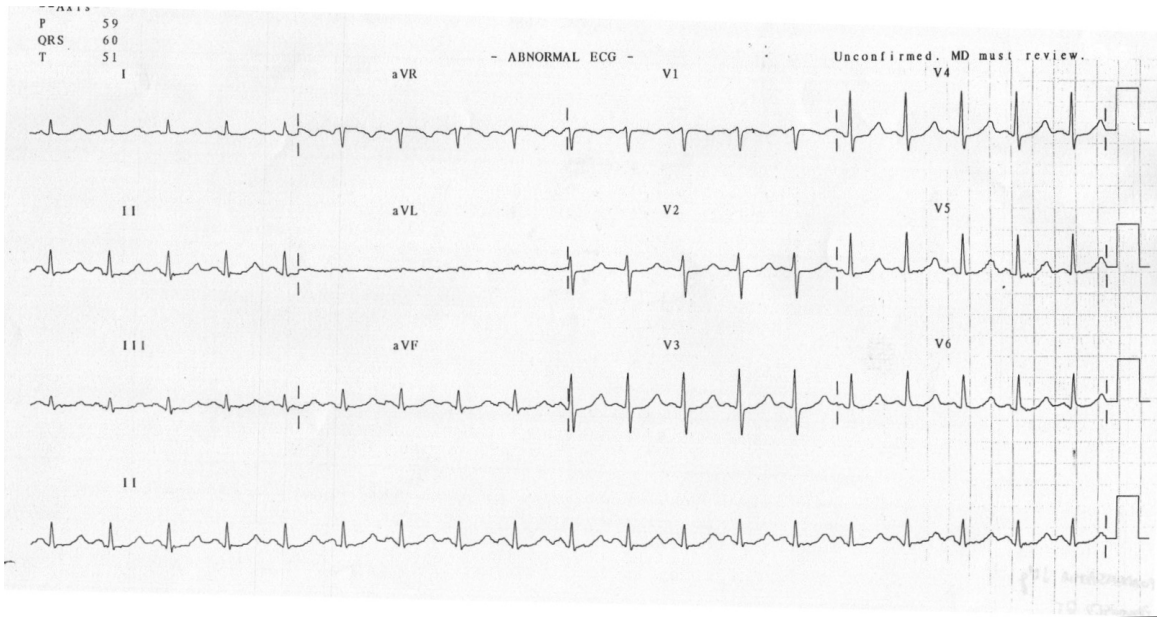
Hypomagnesemia may lead to Hypocalcemia; Ca levels should be checked and addressed when evaluating magnesium values.

Treatment
Immediate treatment
Indications: Ventricular arrhythmia, tetanic muscular spasms

IV: $MgSO_4$ 1-2 g slow IV (diluted in 50-100 mL D5W) over 5-60 minutes, then 0.5-1 g/hr IV

Note: serum magnesium concentration regulates renal magnesium reabsorption. An abrupt elevation in magnesium concentration may reduce magnesium retention resulting in paradoxical urinary excretion. Thus serum levels should be checked frequently to ensure stabilization.

Identification of EKG Abnormalities Consistent with Hypokalemia (EPA-3)



Scenario: Patient with enteritis and diarrhea; chronic pancreatitis (saponification of Mg and Ca); Proton pump inhibitor use in peptic ulcer disease; renal losses from diuretic use (thiazides); chronic alcohol abuse

ECG (Hypomagnesemia)

(Source: http://cdn.lifeinthefastlane.com/wp-content/uploads/2011/03/ECG90402-Hypomagnesaemia_prolonged-QT.jpg)

Note: Hypomagnesemia is commonly seen with hypokalemia; both values should be checked; higher risk of ventricular tachyarrhythmias

ECG findings:
Ectopy
Prolonged QT interval
Tachyarrhythmias (ex: torsades de pointes)

HYPERCHLOREMIA

Causes:
Dehydration
Diarrhea (loss of HCO3)
Renal insufficiency (RTA, nephrotic syndrome)
Diuretics (HCTZ, Acetazolamide-induced hyperchloremic acidosis)

Lab Tests: Basic metabolic panel, including glucose, creatinine; consider LFTs (albumin)
Serum anion gap = Measured cations - Measured anions

Serum anion gap = Na - (Cl + HCO3)
Note: 'Normal values vary from lab to lab analysis (check your hospital's range); most normal values for the serum anion gap range from 3 to 10 meq/L (averaging 6 meq/L)

Note: Some institutions also incorporate use serum K value in the calculation: Serum anion gap = (Na + K) - (Cl + HCO3)
If used, the normal anion gap range will increase by approximately 4 meq/L

Note: serum albumin is the anion responsible serum anion gap; poor liver function of nephrosis with low albumin will reduce the gap.

Hyperchloremic Metabolic Acidosis (non-anion gap acidosis: unmeasured anions lower, Cl- elevated)
Cause:
Loss of HCO3 (ex: diarrhea; RTA; ileal loop)
Reduced acid loss from kidney (Normal function: sulfuric + phosphoric acid from protein metabolism:
a) Glomerular NaSulfate +NaPhosphate
b) Distal tubular HSulfuric + HPhosphoric [Na saved]
c) Reduced GFR: increased anions (ex: sulfate, phosphate)
d) Tubular dysfunction: reduced H excretion

RTA (Type 1, 'Distal') reduced H excretion; sulfates and phosphates are already filtered so no unmeasured anion retention thus normal anion gap
Reduced Aldosterone
Treatment:
Hydration solutions containing bicarbonate, acetate, citrate, or phosphate salts in exchange for chloride. Bicarbonate replacement of 1-2 meq/kg/day with a goal serum HCO3 value 22-24 meq/L. Serum K is also commonly low in distal RTA. Addition of K citrate as needed.

RTA (Type 2, 'Proximal') reduced proximal bicarbonate reabsorption resulting in reduced serum bicarbonate concentration. Increases in filtered bicarbonate load above the reduced reabsorptive capacity, resulting in a metabolic acidosis. Example includes Fanconi Syndrome; reduced proximal tubular function results in phosphaturia, glycosuria, proteinuria.
Treatment:
Bicarbonate supplementation (10 to 15 meq/kg/day); close monitoring of serum K and addition on potassium citrate as needed.

HYPOCHLOREMIA

Causes:
Vomiting,
Diarrhea,
Gastrointestinal suction,
Diuretics,
Syndrome of inappropriate antidiuretic hormone secretion, (SIADH),
Water intoxication,

Excessive sweating,
Adrenal insufficiency,
Hyperaldosteronism,
Drugs (ex: laxatives, corticosteroids, bicarbonate)
Lab Tests: Basic metabolic panel, including glucose and creatinine; hypochloremia can occur with significant volume depletion and dehydration with resultant concurrent hypokalemia, hyponatremia, and metabolic alkalosis

Treatment
Resuscitation with chloride rich isotonic fluid, ex: 0.9% normal saline to restore intravascular volume. Following this, maintenance fluid management with judicious correction of concurrent hypokalemia. With restoration of chloride levels however, serum bicarbonate values will return to normal and serum potassium concentration will rise. Frequent checks of the basic metabolic panel may be required.

SPECIAL CONSIDERATIONS

Pediatric Resuscitation

Case example: A 7 year-old child 3 days sp laparoscopic appendectomy arrives after 8 hours of progressive abdominal pain distention and recurrent nonbloody emesis thought related to an adynamic ileus. His vital signs include a heart rate of 140, blood pressure 90/40 respirations 20 O2 sat 100%RA; his abdomen is distended tympanic and mildly tender diffusely without peritonitis or focal tenderness. Your nurse asks if you would like to commence fluid treatment. What is the most appropriate next step?

Aggressive fluid resuscitation using isotonic solution 10-20 mg/kg bolus, pre-emptive assumption of evolved metabolic alkalosis, chloride responsive condition best managed using a saline solution (ex: 0.9%NaCL); after stabilization of vital sings calculation of maintenance infusion (ex: 4-2-1 rule). The risk of concurrent K losses requiring a serum K check as well as consideration of K replacement and its various administration options. If an NG Tube is placed, additional losses must be calculated and added separately to the total input needs (ex: replacement of NGT losses cc for cc every 8-hours, in addition to the 4-2-1 maintenance calculation).

Burns – Adult and Pediatric - Parkland Formula for both Children and Adults

Case example: A 5 year-old child weighing 22kg suffers partial and full thickness burns to the entire left leg, left arm and back in a house fire within the last hour. EMS have placed an IV but have not begun IV resuscitation. The nurse asks you how to proceed.

The Rule of Nines (the child scale age limit is 3 so the Adult formula should be used; but that the formula is somewhat inaccurate and discussions may be useful regarding Lund-Browder Classification), calculate the %TBSA and calculate the resuscitation needs for his given weight and timing (50% within the first 8 hours). Students must also recognize that the formula does not take into consideration the child's maintenance needs (adding volume based upon the 4-2-1 method to calculate the maintenance needs over 24 hours; also utility of colloids may be discussed for TBSA >30%).

MASSIVE TRANSFUSION

Case example: A 22 year-old female arrives after being struck by an automobile. She was found unconscious and unresponsive at the scene with a heart rate of 130 and a BP 82/40 mm Hg. She is intubated and immobilized for transport with 2 peripheral IVs placed and 1 liter of LR running. On arrival; her vital signs are unchanged, her abdomen is distended with an unstable pelvis and a GCS of 7. FAST is positive. The nurse asks you what you would like to do next.

Discussion of the indications for massive transfusion protocol (ex: Assessment of Blood Consumption/ABC score, persistent hemodynamic instability in context, active bleeding requiring operative or IR embolization, ongoing blood transfusion), what the blood bank will require, what types of products, infusion rate and product ratios [ex: 2:1 – 1:1]) should be given.

Questions

1. A 55 year-old 70kg patient with a history of cholelithiasis presents with 2 days of progressive epigastic abdominal pain, fever, anorexia, episodes of nonbloody, nonbilious emesis. The last bowel movement was 24 hours prior to arrival without hematochezia or melena The patient has the following vital signs: T 101.2, HR 106 BP 96/56 RR 22 100%. The mucous membranes are dry. Lungs are clear, the heart tachycardic but without murmurs or gallops. There is significant and diffuse epigastric tenderness to gentle palpation with an equivocal Murphy's tenderness. Labs reveal an elevated WBC count and leftward shift, elevated amylase, lipase and LFTs. Right upper quadrant ultrasound reveals gallstones with sonographic Murphy's tenderness and a dilated common bile duct of 9mm. As the clinician, you suspect sepsis and request to commence treatment.

   What is the MOST appropriate choice of intravenous fluid therapy?

   A. D5 0.45%NaCl at 110cc/hr
   B. D5 0.45%NaCl + 40meqKCl/L at 110cc/hr
   C. 2 units crossmatched packed red blood cells
   D. 0.9% NaCl, 2.0 liters over 30minutes/1 hour
   E. Lactated Ringers solution 1 liter over 1 hour

2. Paramedics deliver a 27 year-old patient whom they found on the pavement after accidentally falling from the second-story window of his apartment. The patient had an initial heart rate of 134, blood pressure 86/52 and shallow respiratory rate of 20. Two 14-gauge IVs were placed and 2 liters of lactated ringers solution were being infused during transport. On arrival, the patient remains unresponsive with clear equal breath sounds, heart rate of 138, blood pressure of 88/56 with absent radial pulses, multiple contusions and abrasions along the right lower lateral chest and abdominal wall and right hip with ecchymosis in the right groin and perineum. FAST exam is positive and the right iliac wing feels unstable.

   What is the MOST appropriate next step in the resuscitation to stabilize the patient's blood pressure?

   A. Complete the 2 liters of LR and infuse an additional 2 liters; then reassess.
   B. Allow hypotension to persist
   C. Activation of Massive Transfusion Protocol with a ratio of RBC:Plasma of 2:1
   D. Arrange for transfusion of crossmatched blood and FFP, RBC:Plasma ratio of 2:1
   E. Complete the 2 liters of LR and infuse 2 units of type O Rh-negative donor blood.

3. A 27 year-old patient suffers from a gunshot wound to the abdomen involving the liver. His presenting vital signs after a 30-minute transport from the field included heart rates in the 150s and blood pressures of 60s/40s. The patient is managed aggressively and stabilized 3 hours after the event.

   What is the MOST LIKELY effect of this condition on the patient's renal function?

   A. Vasopressor use will spare renal perfusion.

B. Maintained GFR and creatinine clearance should be expected.
C. Hemodilution preserves renal function.
D. As with other tissues, the kidneys can tolerate up to 6 hours of ischemia.
E. Acute renal insufficiency is likely with elevated BUN values despite urine output > 1.0cc/kg/hr.

4. A 65 year-old patient with a history of jejunal-cutaneous fistula requires an admission. The fistula output over the last 24 hours is 1500cc of watery, non-bloody material.

   Which of the following solutions would BEST REPLACE the patient's losses?

	Na(meq)	K	Ca	Cl	HCO3	
A.	39	0	0	39	0	(0.25%NaCl)
B.	154	0	0	154	0	(0.9%NaCl)
C.	130	4	3	109	28	(LR)
D.	77	0	0	77	0	(0.45%NaCl)
E.	513	0	0	513	0	(3%NaCl)

5. You are asked by your senior surgical resident to calculate the maintenance fluid of the patient who is post-operative day 2 from an emergency sigmoid resection for volvulus. The patient is 66 years old with a history of hypertension and has excellent cardiac function. He weighs 70Kg, has an orogastric tube and urinary catheter.

   Which value below is the best estimate of MAINTENANCE FLUID NEEDS for this patient over the next 8 hours?

   A. 650
   B. 780
   C. 880
   D. 950
   E. 1080

Answers

1. **D.** The patient has clinical evidence of inadequate perfusion. The cause of the condition is acute progressive cholangitis from a common biliary duct obstruction. This has progressed from an acute systemic inflammatory response to sepsis. Progressive tissue hypoxia from poor perfusion can lead to progressive base deficit and lactic acidosis. Fluid resuscitation should be initiated as early as possible in patients with severe sepsis. Early recognition of sepsis and septic shock and appropriate fluid resuscitation can improve the patient's outcome. Early goal-directed therapy (EGDT) decreases the in-hospital mortality of patients with sepsis. The Surviving Sepsis Campaign guidelines recommends that septic patients with suspected hypovolemia receive 20-30cc/kg of isotonic crystalloids as soon as possible. Greater volumes may be required. Answer A is neither adequate fluid concentration nor infusion rate. KCl (answer B) should not be administered to patients until adequate volume resuscitation and resumption of urine output has occurred. The patient has no clinical evidence of acute hemorrhage making transfusion inappropriate (answer C). The volume of Lactated Ringers solution is inadequate to resuscitate this 70kg septic patient (answer E).

   References:
   Moore LJ, Moore FA, Jones SL, Xu J, Bass BL: Sepsis in general surgery: a deadly complication. Am J Surg 2009, 198(6):868–874.

   Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Eng J Med 2001, 345:1368–1377.

   Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304-377.

   ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.

   Sartelli et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study; World Journal of Emergency Surgery 20127:36
   DOI: 10.1186/1749-7922-7-36

2. **C**. The patient has persistent tachycardia and hypotension, absent distal pulses with FAST exam evidence of intraperitoneal hemorrhage as well as examination findings of pelvis fracture with concurrent risk of retroperitoneal hemorrhage. The patient has an ABC (Assessment of Blood Consumption) score of 3, suggesting the potential need for massive transfusion of 10 units or more of PRBCs and associated products in order to stabilize ongoing losses. The ABC score has a sensitivity and specificity ranging from 75% to 90% and 67% to 88% with a score of 3 or more. Criteria to consider the need for massive transfusion of red blood cells and plasma include and ABC score >2, persistent hemodynamic instability and active bleeding (positive FAST, pelvis fracture). Continued resuscitation with crystalloid is inappropriate as it not only dilutes both O2 carrying capacity and clotting factors, but can also lead to hypothermia and metabolic acidosis.

The patient has evidence of multiple ongoing bleeding sources from blunt trauma and allowing continued and progressive hypotension carries the risk of progressive tissue hypoxia, worsening base deficit and lactic acidosis. Permissive hypotension is not a treatment. It is never an alternative for definitive hemorrhage control (surgery, embolization), and it currently only applies to trauma patients with active bleeding in the prehospital arena or emergency department while awaiting resuscitation with blood products and emergent surgical intervention.

There is no indication that 2 units of donor blood will be an adequate resuscitation. Appropriate management is to arrange for the possibility of ongoing blood product resuscitation with a RBC:Plasma ratio of 2:1, and capacity to add platelets.

References:

Cotton BA, et. al. Guidelines for prehospital fluid resuscitation in the injured patient. Eastern Association for the Surgery of Trauma (EAST) practice management guideline. J Trauma, 2009; 67(2):389–402.

Rossaint R, et al. Management of bleeding following major trauma: an updated European guideline. Critical Care, 2010; 14: R52.

American College of Surgeons, Committee on Trauma. ATLS: Advanced Trauma Life Support Student Course Manual 9th ed. Chicago, IL: American College of Surgeons, 2012.

3. **E**. Kidneys may tolerate 1-2 hours of ischemia before acute injury evolves. With an acute reversible ischemia, decreased creatinine clearance should be expected transiently. Suspect high-output renal insufficiency from reversible ischemia in the presence of elevating BUN values despite adequate urine output. Suspect severe renal insufficiency in the presence of elevated BUN, reduced creatinine clearance and oliguria. Hemodilution from aggressive crystalloid infusion may lead to worsened tissue hypoxia and ischemic-induced renal insufficiency.

4. **C**. High output fistula are defined as those draining > 500cc/day. Small bowel secretions, bile, and pancreatic secretions serve to neutralize gastric acid secretion. Bile contains sodium and chloride, pancreatic secretions contain sodium and bicarbonate. Jejuna lesions are associated with significant losses of Na, Cl, HCO3. Of the solution choices listed above, Lactated Ringers solution provides the best balance of electrolytes and bicarbonate to assist with replacing these proximal intestinal losses.

5. **C.** In this case the patient who has good cardiac function will typically receive maintenance fluid based on the 4-2-1 algorithm. 4cc/hr for the first 10Kg, 2cc/hr for next 10Kg, and 1cc/hr per Kg thereafter. (4cc x 10) + (2cc x 10) + (1cc x 50)=40 + 20 + 50 = 110cc/hr. At times there is a need for replacement fluids above and beyond the maintenance but that is dictated by kidney function, cardiac function, electrolytes, and overall fluid balance. The key is recognizing that crystalloid fluids are pro-inflammatory and therefore must be administered judiciously.

References

American College of Surgeons, Committee on Trauma. ATLS: Advanced Trauma Life Support Student Course Manual 9th ed. Chicago, IL: American College of Surgeons, 2012.

Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, Mira JP, Dequin PF, Gergaud S, Weiss N, Legay F, Le Tulzo Y, Conrad M, Robert R, Gonzalez F, Guitton C, Tamion F, Tonnelier JM, Guezennec P, Van Der Linden T, Vieillard-Baron A, Mariotte E, Pradel G, Lesieur O, Ricard JD, Hervé F, du Cheyron D, Guerin C, Mercat A, Teboul JL. et al. High versus low blood pressure target in patients with septic shock. NEJM. 2014;370(17):1583–1593. doi: 10.1056/NEJMoa1312173.

Bartels K, Thiele RH, Gan TJ. Rational fluid management in today's ICU. Crit Care. 2013;17:S6. doi: 10.1186/cc12771.

Cecconi M, Corredor C, Arulkumaran N, Abuella G, Ball J, Grounds RM, Hamilton M, Rhodes A. Clinical review: goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. Crit Care. 2013;17:209. doi: 10.1186/cc11823.

Cotton BA, et. al. Guidelines for prehospital fluid resuscitation in the injured patient. Eastern Association for the Surgery of Trauma (EAST) practice management guideline. J Trauma, 2009; 67(2):389–402.

Feldheiser A, Pavlova V, Bonomo T, Jones A, Fotopoulou C, Sehouli J, Wernecke KD, Spies C. Balanced crystalloid compared with balanced colloid solution using a goal-directed haemodynamic algorithm. Br J Anaesth. 2013;110:231–240. doi: 10.1093/bja/aes377.

Gautam B, Neilson EG. Volume Depletion versus Dehydration: How Understanding the Difference Can Guide Therapy. Am J Kidney Dis. 2011 Aug: 58(2): 302-309. PMCID: PMC4096820

Hahn RG. In: Clinical Fluid Therapy in the Perioperative Setting. Hahn RG, editor. Cambridge University Press, New York; 2011. Body volumes and fluid kinetics; p. 127.

Lira A, Pinsky MR. Choices in fluid type and volume during resuscitation: impact on patient outcomes. Ann. Intensive Care. 2014; 4:38 PMCID: PMC4298675

Marik PE, Lemson J. Fluid responsiveness: an evolution of our understanding. Br J Anaesth. 2014;112:617–620. doi: 10.1093/bja/aet590.

Marik PE, Monnet X, Teboul JL. Hemodynamic parameters to guide fluid therapy. Ann Intensive Care. 2011;1:1. doi: 10.1186/2110-5820-1-1.

Moore LJ, Moore FA, Jones SL, Xu J, Bass BL: Sepsis in general surgery: adeadly complication. Am J Surg 2009, 198(6):868–874.

Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg. 2006;93:1069–1076. doi: 10.1002/bjs.5454.

ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.

Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, Early Goal-Directed Therapy Collaborative Group: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Eng J Med 2001, 345:1368–1377.

Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304-377.

Rossaint R, et al. Management of bleeding following major trauma: an updated European guideline. Critical Care, 2010; 14: R52.

Sartelli et al. Complicated intra-abdominal infections in Europe: a comprehensive review of the CIAO study; World Journal of Emergency Surgery 20127:36. doi: 10.1186/1749-7922-7-36

Yates DR, Davies SJ, Milner HE, Wilson RJ. Crystalloid or colloid for goal-directed fluid therapy in colorectal surgery. Br J Anaesth. 2014;112(2):281–289. doi: 10.1093/bja/aet307.

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Algorithms for IV fluid therapy in adults

Algorithm 1: Assessment

Using an ABCDE (Airway, Breathing, Circulation, Disability, Exposure) approach, assess whether the patient is hypovolaemic and needs fluid resuscitation
Assess volume status taking into account clinical examination, trends and context. Indicators that a patient may need fluid resuscitation include: systolic BP <100mmHg; heart rate >90bpm; capillary refill >2s or peripheries cold to touch; respiratory rate >20 breaths per min; NEWS ≥5; 45° passive leg raising suggests fluid responsiveness.

Yes → **Algorithm 2: Fluid Resuscitation**

No →

Assess the patient's likely fluid and electrolyte needs
- History: previous limited intake, thirst, abnormal losses, comorbidities.
- Clinical examination: pulse, BP, capillary refill, JVP, oedema (peripheral/pulmonary), postural hypotension.
- Clinical monitoring: NEWS, fluid balance charts, weight.
- Laboratory assessments: FBC, urea, creatinine and electrolytes.

Can the patient meet their fluid and/or electrolyte needs orally or enterally?

Yes → **Ensure nutrition and fluid needs are met**
Also see Nutrition support in adults (NICE clinical guideline 32).

No →

Does the patient have complex fluid or electrolyte replacement or abnormal distribution issues?
Look for existing deficits or excesses, ongoing abnormal losses, abnormal distribution or other complex issues.

Yes → **Algorithm 4: Replacement and Redistribution**

No → **Algorithm 3: Routine Maintenance**

Give maintenance IV fluids
Normal daily fluid and electrolyte requirements:
- 25–30 ml/kg/d water
- 1 mmol/kg/day sodium, potassium*, chloride
- 50–100 g/day glucose (e.g. glucose 5% contains 5 g/100ml).

Reassess and monitor the patient
Stop IV fluids when no longer needed.
Nasogastric fluids or enteral feeding are preferable when maintenance needs are more than 3 days.

Algorithm 2: Fluid Resuscitation

Initiate treatment
- Identify cause of deficit and respond.
- Give a fluid bolus of 500 ml of crystalloid (containing sodium in the range of 130–154 mmol/l) over less than 15 minutes.

Reassess the patient using the ABCDE approach
Does the patient still need fluid resuscitation? Seek expert help if unsure

Yes → >2000 ml given?

No → **Does the patient have signs of shock?**

Yes → **Seek expert help**

No →

>2000 ml given?

Yes → **Seek expert help**

No → **Give a further fluid bolus of 250–500 ml of crystalloid**

Give a further fluid bolus of 250–500 ml of crystalloid → **Reassess the patient using the ABCDE approach**

Algorithm 4: Replacement and Redistribution

Existing fluid or electrolyte deficits or excesses
Check for:
- dehydration
- fluid overload
- hyperkalaemia/ hypokalaemia

Estimate deficits or excesses.

Ongoing abnormal fluid or electrolyte losses
Check ongoing losses and estimate amounts. Check for:
- vomiting and NG tube loss
- biliary drainage loss
- high/low volume ileal stoma loss
- diarrhoea/excess colostomy loss
- ongoing blood loss, e.g. melaena
- sweating/fever/dehydration
- pancreatic/jejunal fistula/stoma loss
- urinary loss, e.g. post AKI polyuria.

Redistribution and other complex issues
Check for:
- gross oedema
- severe sepsis
- hypernatraemia/ hyponatraemia
- renal, liver and/or cardiac impairment.
- post-operative fluid retention and redistribution
- malnourished and refeeding issues

Seek expert help if necessary and estimate requirements.

Prescribe by adding to or subtracting from routine maintenance, adjusting for all other sources of fluid and electrolytes (oral, enteral and drug prescriptions)

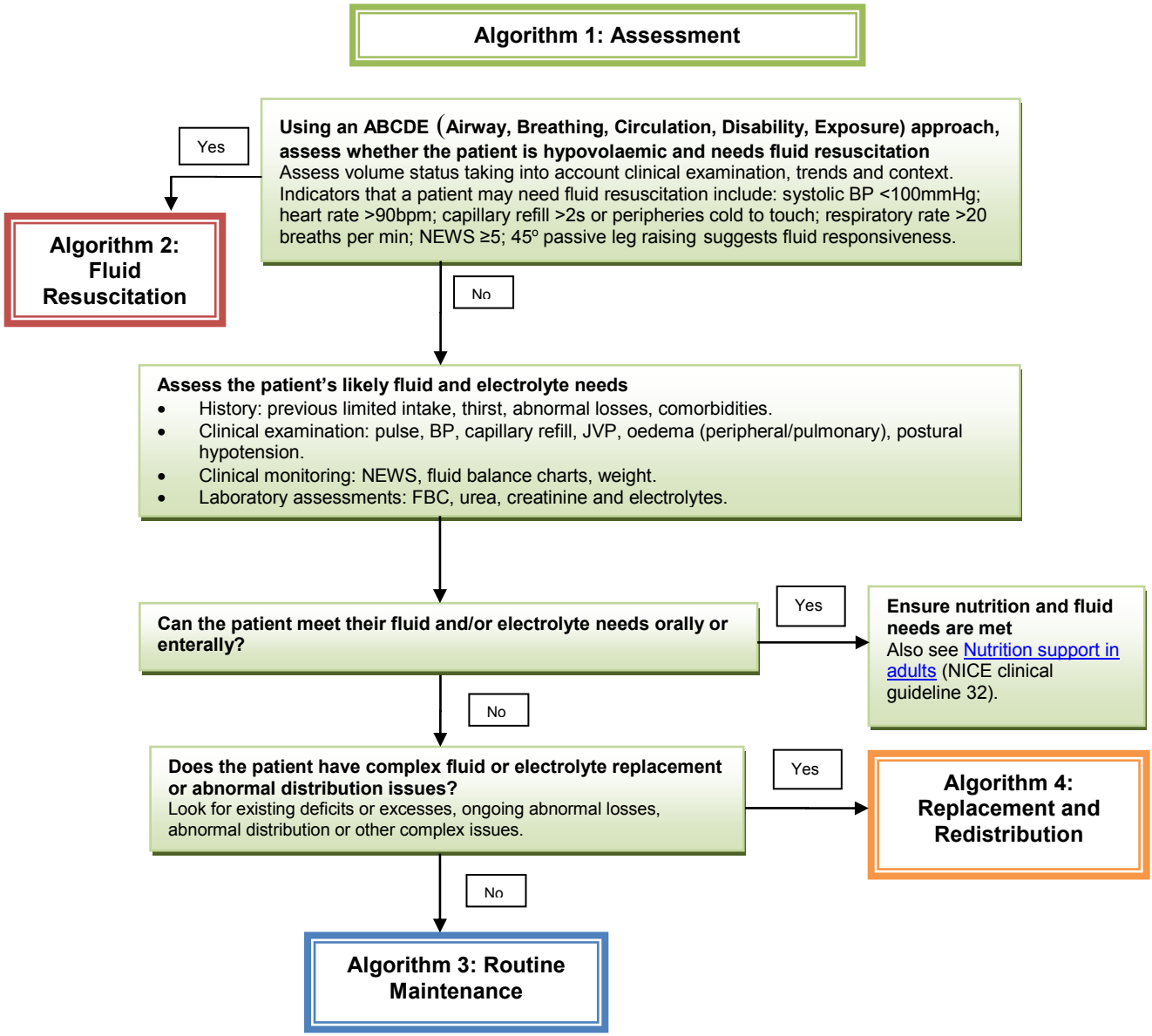
Monitor and reassess fluid and biochemical status by clinical and laboratory monitoring

*Weight-based potassium prescriptions should be rounded to the nearest common fluids available (for example, a 67 kg person should have fluids containing 20 mmol and 40 mmol of potassium in a 24-hour period).

Potassium should not be added to intravenous fluid bags as this is dangerous.

'Intravenous fluid therapy in adults in hospital', NICE clinical guideline 174 (December 2013. Last update December 2016)

Algorithms for IV fluid therapy in adults



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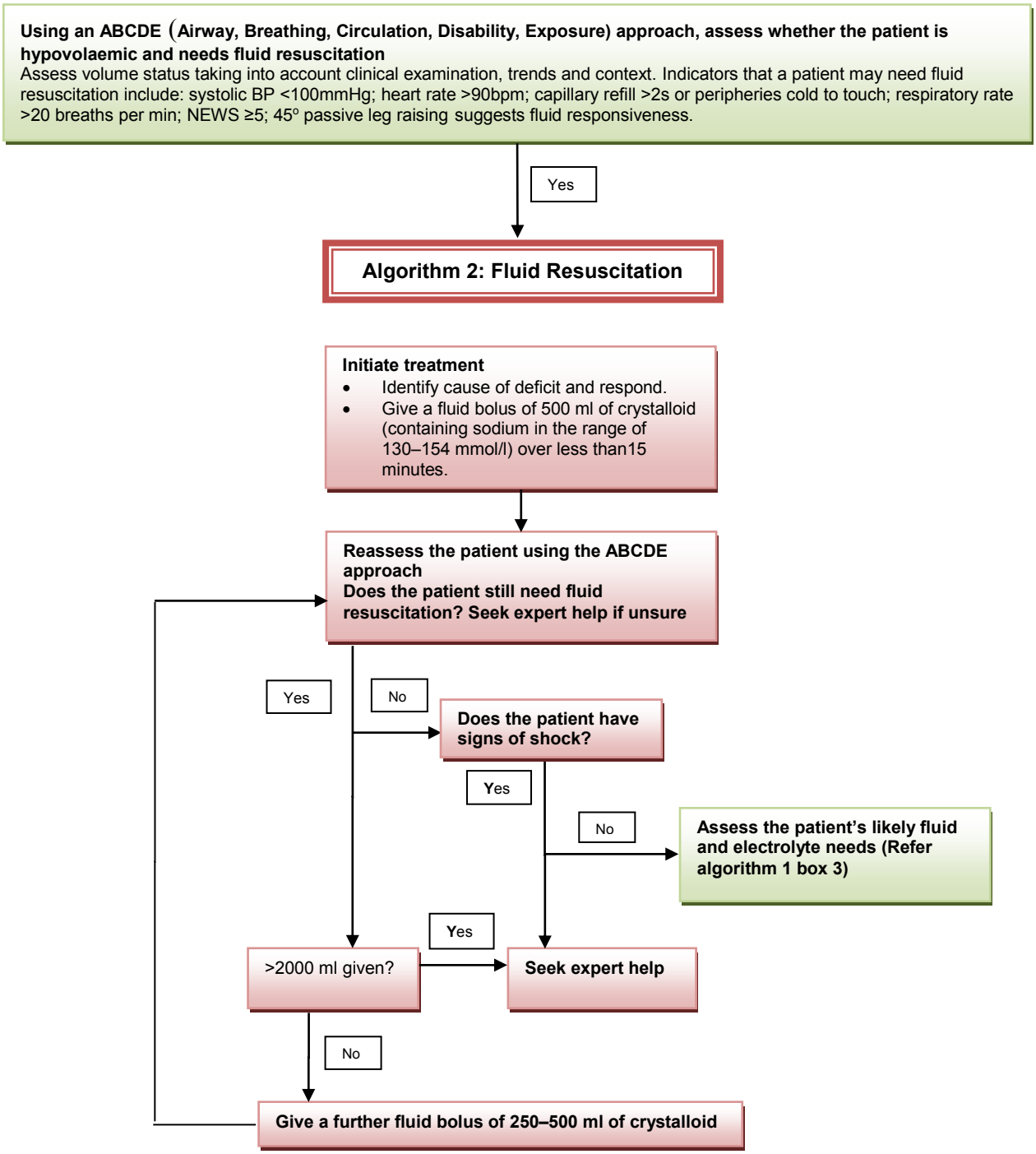

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NICE National Institute for Health and Care Excellence

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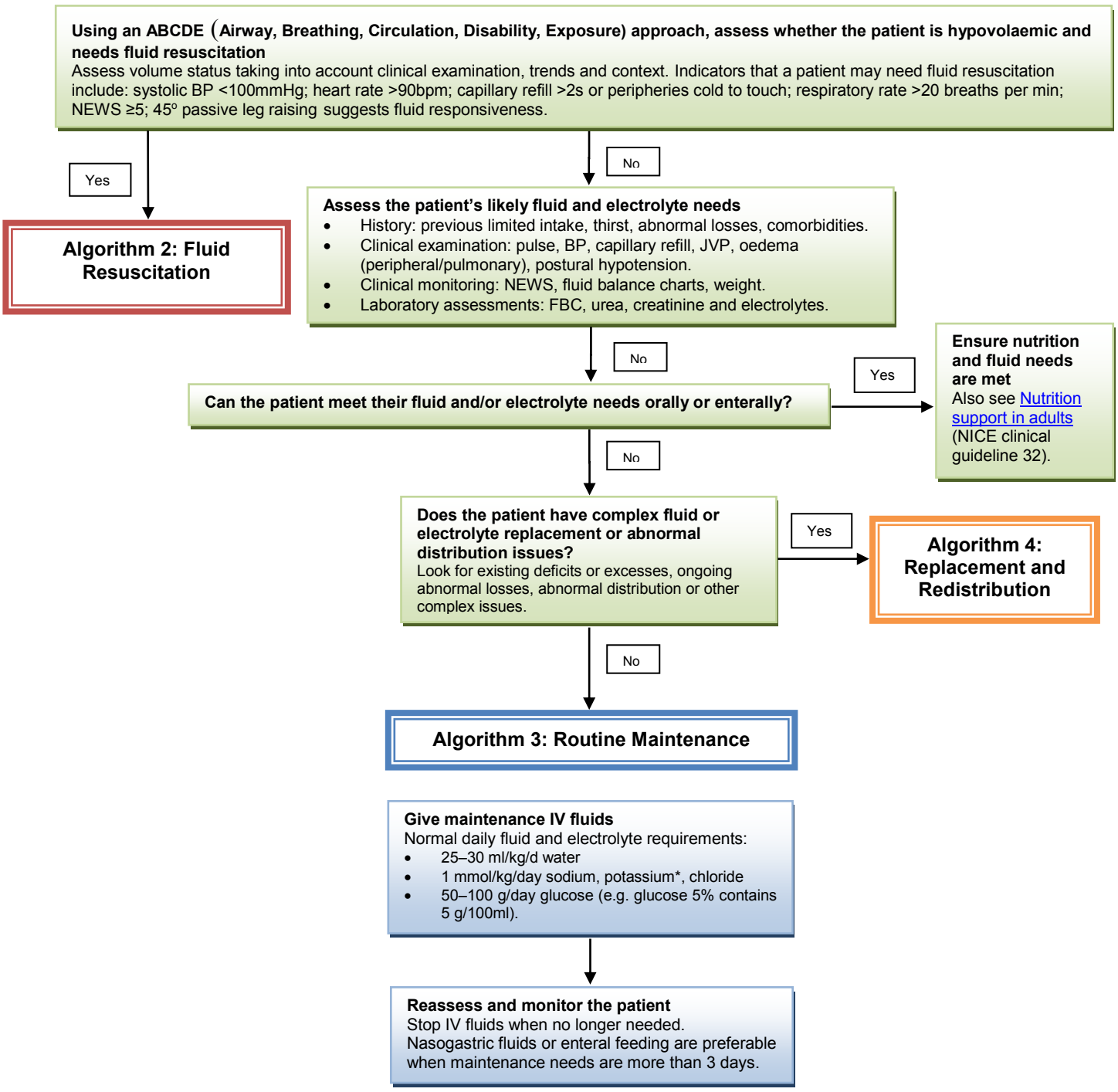

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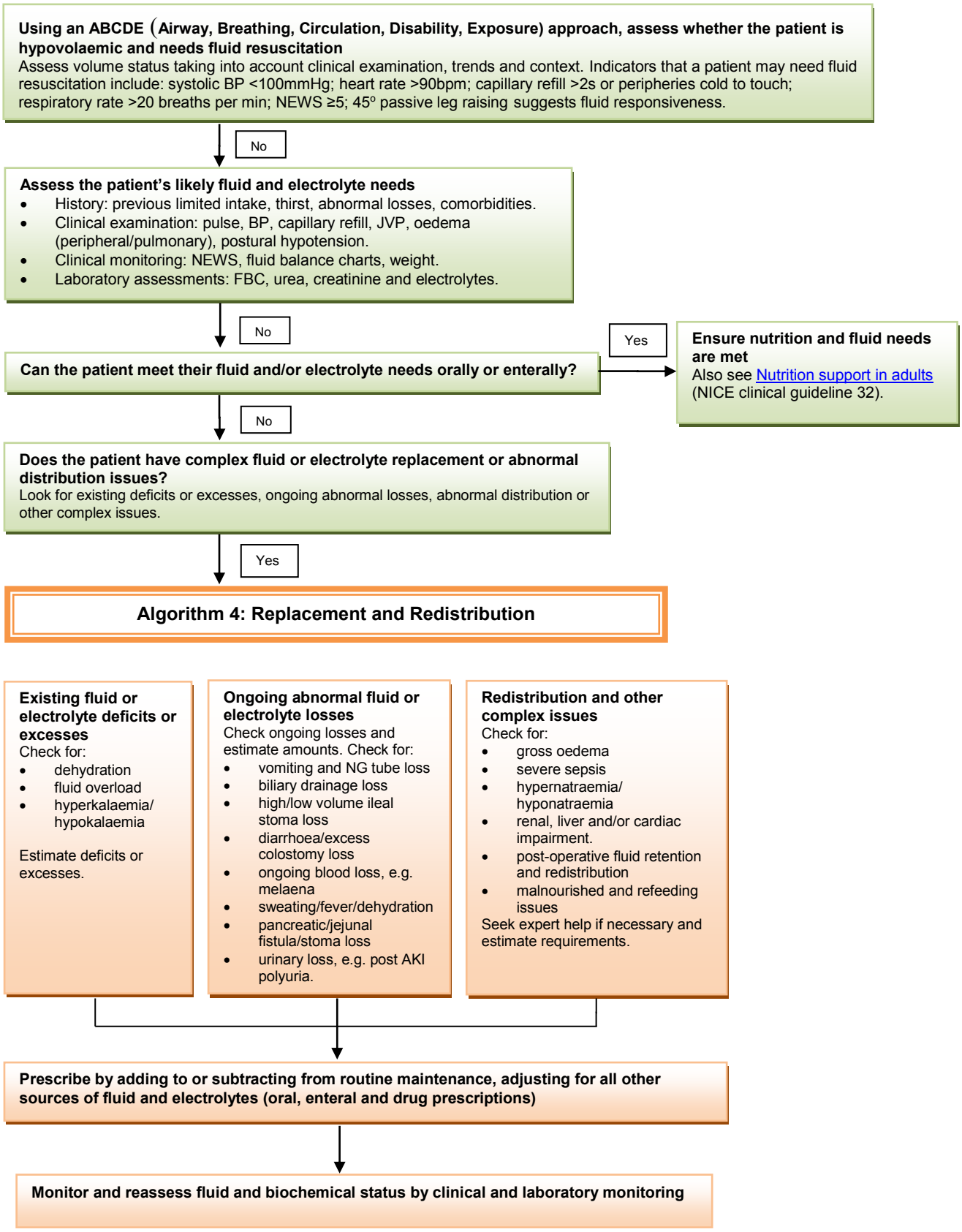

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