INTRAVENOUS FLUIDS

(a) ***To describe the composition, pH, and osmolality of crystalloids and colloids used in clinical practice.***

(b) ***To evaluate their effects and fate when used in volume replacement.***

(c) ***To compare the pharmacology of colloids such as albumin, gelatin derivatives, polysaccharide derivatives and starch solutions with crystalloids such as lactate solutions and normal saline.***

(I) Composition of 1L fluids:

Fluid type	Na^+ (mmol)	K^+ (mmol)	Ca^{2+} (mmol)	Mg^{2+} (mmol)	Cl^- (mmol)	Other	Osmolarity (mosm/L)	pH
Crystalloids								
0.9% saline	154	-	-	-	154	-	308	5.0
3% saline	513	-	-	-	513	-	1027	5.0
5% dextrose	-	-	-	-	-	Glucose 50 g/L	278	4.0
4% dex. + 1/5 N/S	31	-	-	-	31	Glucose 40 g/L	282	4.5
Hartmann's	131	5	2	-	111	Lactate 29 mmol	279	6.5
Plasmalyte 148	140	5	-	3	98	Acetate 27 mmol Gluconate 23 mmol	294	5.5
Mannitol 20%	-	-	-	-	-	Mannitol 200 mg	1098	-
8.4% $NaHCO_3$	1000	-	-	-	-	HCO_3^- 1000 mmol	2000	8.0
Colloids								
Gelofusine	154	0.4	0.4	0.4	125	Gelatin 40 g/L	274	4.0
Voluven 6%	154	-	-	-	154	Starch 60 g/L	310	5.5
Albumin 4.5%	< 160	< 10	-	-	< 160	Albumin 45 g	< 300	6.9
Albumin 20%	< 120	< 2	-	-	< 40	Albumin 200 g	135	6.9
Haemaccel 3.5%	145	5.1	6.25	-	145	Gelatin 35 g	301	7.3
Dextran	Dextran 40 (100 g/L of dextran with avg. MWT 40 kDa in 0.9% saline or 5% dextrose) Dextran 70 (60 g/L of dextra with avg. MWT 70 kDa in 0.9% saline or 5% dextrose)							

(II) Crystalloid fluid:

Types of crystalloid fluids:

- (1) Replacement fluids
  - Used for intravascular volume (IVV) expansion → BUT requires 3-4x volume of blood volume loss as replacement (Ie. 1L BV loss requires 3-4L replacement with crystalloids) → this is because crystalloids:
    - (i) Expand ECF compartment volume only → because they have similar (or slightly ↑) osmolality and tonicity as ECF due to their $[Na^+]$
    - (ii) Distribute between ISF and plasma in 3:1 proportion (Ie. only ¼ remains in IVV) → because they lack any oncotic pressure
  - Types of fluids used – Hartmann's, 0.9% saline, Plasmalyte 148
- (2) Maintenance fluids
  - Used to maintain daily requirements for H_2O (25-35 mL/kg/day), electrolytes (Na^+ 1-1.5 mmol/kg/day, K^+ 0.7-0.9 mmol/kg/day, Ca^{2+} 5 mmol/day, Mg^{2+} 0.5 mmol/day) and glucose
  - Generally iso-osmotic and isotonic → do not cause haemolysis
  - Types of fluids used – 5% dextrose, 4% dex. + 1/5 N/S, 0.9% saline + KCl (alt. can use Hartmann's or Plasmalyte 148 also)
- (3) Special fluids – Hypertonic (3%) saline, 8.4% HCO3, Mannitol 20%

Specific crystalloid fluids:

- (1) Saline (0.9%/3%)
  - Used for (i) IVV replacement (0.9% and 3%), (ii) maintenance fluids (0.9%), (iii) correction of ↓ Na^+ (3%)
  - Remains in IVV for 30 mins (then distributes throughout EC space)
  - Issues:
    - (i) Hyperchloraemic metabolic acidosis (esp with renal insufficiency) due to ↑ high Cl^- content
    - (ii) Hypernatraemia due to ↑ higher Na^+ content (cf. plasma)
    - (iii) ↑ plasma osmolality due to ↑ higher Na^+/Cl^- content (cf. plasma)
    - (iv) Cerebral pontine demyelinosis (only with 3%)
    - Note → above issues more common with 3% saline
- (2) 5% dextrose
  - Used as maintenance fluid and providing calories (glucose)
  - Cannot be used as replacement fluids → because it remains very briefly in IVV, then rapidly redistributes within TBW in proportion (mainly intracellularly) as glucose is taken up avidly by cells (via insulin) for metabolism → fluid effectively becomes "pure H_2O"
  - Main issues is hyponatraemia and cellular oedema (rarely causes hyperglycaemia)
- (3) Hartmann's
  - Used for both replacement and maintenance fluid therapy
  - Remains in IVV for 30 mins (then distributes throughout EC space)
  - Contains:
    - (a) Lactate → metabolised in liver (over 2 hrs) to produce equivalent amounts of HCO_3^- and dextrose → (i) useful in providing calories, and (ii) does NOT contribute to acidosis (as lactate (conjugate base) is given with Na^+, and not H^+ so it cannot form lactic acid (acid); it also forms HCO_3^-)
    - (b) ↓ Cl^- content → avoid hyperchloraemic metabolic acidosis a/w N/S
    - (c) Contains Ca^{2+} and K^+ → useful for electrolyte maintenance
  - Issues:
    - (i) Lactate → cannot be given with liver disease (lactate accumulation)
    - (ii) K^+ → risk of ↑ K^+ (esp with renal disease)
    - (iii) Ca^{2+} → binds to citrate (anticoagulant) in stored blood → can lead to clotting of blood in IV giving set
    - (iv) Metabolic alkalosis
- (4) Plasmalyte 148
  - Similar to Hartmann's except it contains:
    - (i) Mg^{2+} (instead of Ca^{2+}) → can be given with stored blood
    - (ii) Acetate and gluconate (instead of lactate) as HCO_3^- precursors → does not accumulate with liver disease as they are also metabolised by kidneys to HCO_3^-. Also does not contribute to acidosis for same reasons as Hartmann's
    - (iii) ↑ Na^+ content and ↑ osmolality → hypernatraemia and ↑ plasma osmolality (but less so cf. N/S)
    - (iv) Even ↓ Cl^- cf. Hartmann's
- (6) Mannitol 20%
  - Mannitol is LMWT monosaccharide (182 Da) used for:
    - (i) ↓ raised ICP (Ie. due to SOL)
    - (ii) Renal protection (Ie. osmotic diuresis preserves peri-op. renal function 2° jaundice or vascular surgery, and protects against ARF with rhabdomyolysis)
    - (iii) Short-term management of acute glaucoma (Ie. ↓ IOP)
    - (iv) Initiate diuresis with renal transplant

    - It is given IV 1 g/kg for raised ICP over 15 mins (prior to surgery) +/- 0.25-0.5 g/kg intermittent doses. Diuretic dose is IV 0.5-1 g/kg
    - Biphasic distribution to plasma and EC water → Vd 0.47 L/kg
    - Clearance (7 mL/min/kg) → It is not metabolised, but instead excreted unchanged in urine (elimination t ½ 72 mins)
- (5) $NaHCO_3$
    - Used to (i) correct hyperkalaemia and (ii) treat metabolic acidosis

Advantages of crystalloids:
- (1) Inexpensive and easy to store with long shelf-life → readily available
- (2) Very low incidence of adverse reactions (esp anaphylactoid and histamine release)
- (3) Effective as both replacement and maintenance fluids
- (4) No special compatibility testing required or religious objections to use

(II) Colloid fluids:

Overview of colloid fluids:
- Colloid fluids are used for IVV expansion and can replace equivalent amounts of blood volume loss (Ie. 1 L colloids can replace 1L of BV loss)
- This is because they contain large MWT substances (> 30 kDa) that exert oncotic pressure similar to (or ↑) than plasma → causes fluids to remain within intravascular compartment only
- Colloids have two types of MWTs quoted by manufacturers:
    - (i) Mw (weight average MWT) → via complex calculations → indicates viscosity
    - (ii) Mn (number average MWT) → = total weight of molecules/total # of molecules → indicates oncotic pressure

> Nb. Albumin has Mw = Mn b/c all molecules have same MWT (monodisperse), while artificial colloids has Mw ≠ Mn b/c molecules have a with range of MWT (polydisperse)

Types of colloid fluids:
- (1) Albumin (4.5% or 20%)
    - Derived from human plasma → treated by heating to 60 °C for 10 hrs → eliminates risk of disease transmission
    - Cf. other colloids, its role includes → (i) Transport function (bilirubin, FFAs, Ca^{2+}, thyroid hormone, cortisol, acidic drugs), (ii) Main contributor of plasma oncotic pressure (60-80%) due to ↑ plasma [ ] (40 g/L), ↓ MWT (69 kDa) and –ve charge (Gibbs-Donnan effect), and (iii) Cellular metabolism of a.a.
    - Expands IVV for ~ 24 hrs → majority (50-60%) exists in extravascular space (40-60% intravascular) as it gradually enters ISF from capillaries (via pinocytosis) → metabolised by tissue cells or returned to circulation via lymphatics
    - t ½ of 20 days → metabolised by liver, kidneys, gut
    - Issues → (i) Risk of anaphylaxis/anaphylactoid reactions, and (ii) Higher cost cf. crystalloids
- (2) Artificial colloids
    - (a) Dextrans
        - Highly branched polysaccharides produced using bacteria (containing dextran sucrase) grown in sucrose medium
        - Two types → (i) Dextran 40 (Mw 40k, Mn 25k) → good for ↓ blood viscosity (as ↓ Mw), (ii) Dextran 70 (Mw 70k, Mn 39k) → good for IVV expansion (as ↑ Mn and ↑ t ½ in IV space)

- Expands IVV for 2-4 hrs (dextran 40) or ~ 12 hrs (dextran 70) → metabolised by dextrinases (liver, lung, kidney, spleen) and also renally excreted unchanged (esp dextran 40 as tubular T_{MAX} ~ 55 kDa)
- Issues:
  - (i) ↑↑↑ risk of severe anaphylaxis (1:3000) → due to "dextran reactive Ab's" → can ↓ incidence with hapten pre-treatment
  - (ii) Histamine release
  - (iii) Liver storage → limit max dose of 20 mL/kg (1.5 L)
  - (iv) Impaired haemostasis → induces acquired vWB state and platelet dysfunction
  - (v) Interferes with cross-matching (due to rouleaux formation)
  - (vi) Higher cost cf. crystalloids

- (b) Gelatin
  - Large MWT protein formed from animal CT (Eg. cattle bone/collagen) → alkalinise, then thermally degrade (dissolve in boiling H_2O), then cool to form new inter-chain bonds (Eg. succinylated, urea cross link, Etc. → depending on chemical conditions)
  - Older gelatins had either (i) ↑ MWT (100 kDa) → good oncotic effect/IVV expansion BUT ↑ viscosity and solidification at lower temperatures, or (ii) ↓ MWT → ↓ viscosity/gelatinisation issue but poor oncotic effect/IVV expansion
  - Modern gelatins have intermediate MWT (35 kDa) → compromise between oncotic pressure and melting point → 3 types exist:
    - (i) Succinylated gelatin (Eg. gelofusine)
    - (ii) Urea-crosslinked gelatin (Eg. polygeline or haemaccel)
    - (iii) Oxypolygelatin (Eg. gelifundol)
  - Expands IVV for 4-6 hrs → metabolised by liver and also excreted unchanged by kidneys. It is NOT stored in body (cf. dextrin/starches)
  - Also isotonic, contains ↓ Cl^-, and as some K^+, Mg^{2+}, Ca^{2+} (cf. starches)
  - Issues:
    - (i) Anaphylaxis/anaphylactoid reactions (1:10,000)
    - (ii) Histamine release
    - (iii) Coagulopathy due to haemodilution
    - (iv) Higher cost cf. crystalloids
- (c) Hydroethylstarches (HES)
  - Produced from amylopectin and stabilised by hydroxyethylation to form a highly branched starch → (i) ↑ soluble and (ii) ↓ metabolism (↑ t ½ due to ↑ resistance to amylase)
  - Several types of HES depending on → (i) [HES], (ii) Mwt of HES, and (iii) degree of substitutions (C2:C6 ratio) → HMWT HES have longest DOA (↑ t ½) but most side-effects while LMWT HES have very short DOA. Medium MWT HES (Eg. Hetastarch or voluven 6% or 10%; 450 kDa) provides the best balance
  - Expands IVV for ~ 24 hrs → cleared from circulation via plasma amylase metabolism, renal excretion unchanged, or redistribution (taken up by reticulo-endothelial system)
  - Issues:
    - (i) Anaphylaxis/anaphylactoid reactions rarer (1:20,000)
    - (ii) Severe pruritis due to storage in RE system
    - (iii) Higher cost cf. crystalloids
    - (iv) Coagulopathy (↓ vWF, CF VIII and fibrinogen levels; platelet dysfunction)
    - (v) Renal dysfunction (renal tubular swelling/tubular obstruction)

- (vi) ↑ osmolality and Cl^- content cf. other colloids

Properties on an ideal colloid fluid:

- Physico-chemical:
  - Iso-oncotic and isotonic with plasma
  - Inexpensive with easy storage (long t 1/2) → Readily available
  - No limits on volume that can be infused
  - No interference with blood grouping/cross-matching
  - Accepted by all patients (Ie. no religious objections)
- Pharmacokinetic:
  - Distributed to intravascular compartment only
  - t ½ 6-12 hrs → sustained IVV expansion
  - Organ independent metabolism and elimination of colloid
  - Not stored in body
  - Active but non-toxic metabolites → prolong colloid effect with toxicity
- Pharmacodynamic
  - Achieves adequate haemodynamic effect (↑ C.O./BP and tissue perfusion)
  - No organ dysfunction (esp with repeated administration)
  - Non-pyrogenic, non-allergic, non-antigenic → low anaphylactoid risk and histamine release
  - No interference with haemostasis/coagulation
  - No agglutination or RBC damage → interferes with cross-matching
  - No acid/base disorders
  - Does not promote infections (bacterial, viral, protozoal)

(III) <u>Body handling of 1000 mL of IV fluids</u>:

Remember:
- TBW (42L in 70 kg man) → 33% ECF (14L) and 66% ICF (28L) → ECF:ICF is 1:2
- ECF → 25% PV (3L) and 75% ISF (11L) → PV:ISF is 1:3
- BV = 5 L and plasma osmolality = 290 mosm/kg
- Baroreceptors respond to 7-10% Δ in BV
- Osmoreceptors respond to 1-2% Δ in plasma osmolality

Body handling of 1000 mL of 5% dextrose:

- Haemodynamic effects (↑ MSFP/RAP → ↑ preload (via FS-effect) → ↑ CO and BP) occurs with very rapid infusions but is very short-lived → this is because fluid is rapidly lost from IVV as it is rapidly distributed to ISF as per Starling forces (as has $P_{ONCOTIC} = 0$)
- Fluid is iso-osmolar and isotonic to plasma → BUT glucose is rapidly taken up into cells (via insulin) and metabolised → fluid becomes hypo-osmolar and isotonic (like "pure H_2O") → distributes throughout TBW compartments in proportion (esp intracellularly):

  1000 mL D5W → 670 mL ICF (66%) and 330 mL ECF (33%) → 250 mL ISF (75%) and 80 mL PV (25%)

- ↑ ICFV and ISFV → but does not cause cellular swelling or interstitial oedema (as lymphatics drain excess fluid back to circulation)
- BV ↑ from 5000 mL to 5080 mL (Δ BV < 2%) → does not trigger BRR
- Plasma osmolality ↓ by 7 mosm/L (= 287 – (287 x 3L/3.08L)) or 2.5% → triggers osmoreceptor → ↓ ADH decrease → ↑ renal H_2O excretion to clear D5W from body

Note → ADH response delayed by ~ 1 hr (3-4x t ½ → t ½ ADH = 15 mins)

Body handling of 1000 mL of 0.9% saline:

- Haemodynamic effects (↑ MSFP/RAP → ↑ preload (via FS-effect) → ↑ CO and BP) occurs with acute ↑ in IVV → this is influenced by:
    - (i) Rate of infusion speed → ↑ infusion = ↑ haemodynamic effects
    - (ii) Vascular compensatory mechanisms → (a) Venodilation (↑ venous pooling in capacitance vessels), (b) ↑ fluid loss to ISF 2° to ↑ capillary $P_{HYDROSTATIC}$, (c) pressure diuresis/natriuresis (↑ urine excretion) → very effective at minimising haemodynamic effects!
    - (iii) Rate at which it is lost form IVV (See below) → ↑ loss from IVV = ↓ haemodynamic effects
- Fluid has similar [Na^+] to ECF → limits distribution to ECF only and distributes within it in proportion:

    1000 mL N/S → 0 mL ICF (0%) and 1000 mL ECF (100%) → 750 mL ISF (75%) and 250 mL PV (25%)

- ↑ ICFV and ISFV → but does not cause cellular swelling or interstitial oedema (as lymphatics drain excess fluid back to circulation)
- Fluid excretion does not depend on hormonal mechanisms because:
    - (i) BV ↑ from 5 L to 5.25 L (Δ BV 5% only) → does not trigger BRR
    - (ii) Plasma osmolality unchanged as N/S is isotonic/iso-osmotic → does not trigger osmoreceptors
- Instead, fluid excretion is dependent on "glomerulotubular imbalance" as follows:
    - N/S has $P_{ONCOTIC} = 0$ (as it has no proteins) → so plasma $P_{ONCOTIC}$ is ↓ slightly → this causes:
        - (i) Fluid shift from IVV to ISF due to Starling's forces
        - (ii) Glomerulotubular imbalance → ↓ plasma $P_{ONCOTIC}$ favours ↑ GFR and ↓ tubular reabsorption of H_2O/Na^+ → ↑ urine production
        - (iii) ISF fluid then redistributes backs into IVV → kidney excretes it as above process until all transfused fluid is excreted and plasma $P_{ONCOTIC}$ normalised

> Note → Excretion of N/S from body is FASTEST (cf. D5W or colloids) as it is does not rely on slow hormonal response mechanisms (Ie. ADH effect)

Body handling of 1000 mL of colloids:

- Colloids remain only in IVV as they are usually iso-oncotic and isotonic to plasma:

    1000 mL colloids → 0 mL ICF (0%) and 1000 mL ECF (1000%) → 0 mL ISF (0%) and 1000 mL PV (100%)

- BV ↑ from 5 L to 6 L (20% ↑ BV) → causes:
    - (i) Significant haemodynamic effects (↑ MSFP/RAP → ↑ preload (via FS-effect) → ↑ CO and BP) → BUT minimised by vascular compensatory mechanisms → (a) Venodilation (↑ venous pooling in capacitance vessels), (b) ↑ fluid loss to ISF 2° to ↑ capillary $P_{HYDROSTATIC}$, (c) pressure diuresis/natriuresis (↑ urine excretion)
    - (ii) Activation of baroreceptors → ↓ ADH release → ↑ renal H_2O excretion to clear extra fluid from the body
- Plasma $P_{ONCOTIC}$ ↑ 2° to net H_2O loss from renal excretion (without loss of colloid from body) → then favours IVV fluid retention due to:
    - (i) Fluid redistribution from ISF to IV space
    - (ii) ↓ GFR and ↑ tubular reabsorption of H_2O/Na^+ → ↓ urine production
    - (iii) Retards inhibition of ADH release (↓ H_2O excretion from body) 2° delayed ↑ plasma osmolality

- Plasma osmolality initially unchanged → BUT ↑ with ↑ plasma $P_{ONCOTIC}$ → retards ↓ ADH release 2° to BRR activation → minimises renal H_2O retention

> Note:
> - Effects on BV are pronounced and prolonged (cf. N/S or D5W) → because colloids are slowly cleared (metabolised/excreted/redistributed)
> - Pressure-volume/osmolality reflex mechanisms involving ADH are more vital in LT regulation of BV (despite being slow in onset of effect) → because Δ BV are significant and more prolonged

> Note → These responses are similar to those when 1000 mL of blood is given → EXCEPT colloids lack O_2 carrying capacity of blood → hence, they cause ↓ [Hb] due to haemodilution

(IV) <u>Body handling of special solutions</u>:

Body handling of 500 mL mannitol 20%:

- Mannitol 20% causes a net fluid shift into intravascular space from ISF/ICF due to an osmotic pressure gradient established by:
  - (i) Mannitol being an obligate EC solute → it does NOT cross cell membranes
  - (ii) Mannitol 20% being hypertonic
- Effect of 500 mL infusion of 20% mannitol:

Pre infusion:
- TBW = 42 L
- Total body solute = 42 L x 290 = 12180 mosm
- ECF solute = 14 L x 290 = 4060 mosm
- ICF solute = 28 L x 290 = 8120 mosm

Post-infusion:
- TBW = 42 L + 0.5 L = 42.5 L
- Total body solute = 12180 + (1098/2) = 12729 mosm
- ECF solute = 4060 + (1098/2) = 4609 mosm
- ICF solute = 8120 mosm (same)

So:
- Plasma osmolarity = 12729 mosm/42.5 L = 300 mosm/L
- ECFV = 4609 mosm/300 mosm/L = 15.4 L
- ICFV = 8120 mosm/300 mosm/L = 27.1 L

- Net effect is:
  - ↓ ICFV by 0.9 L → affects brain cells (dehydration → confusion/obtundation)
  - ↑ ECFV by 1.4 L → 1.05 L in ISF and 0.35L in PV
    - ↑ ISFV does not cause oedema → handled by lymphatic system
    - ↑ BV by 7% → triggers BRR → (i) Inhibits ADH secretion → renal H_2O excretion, and (ii) Stimulates ANP release and inhibits RAAS → natriuresis and diuresis (lose Na^+/H_2O)
  - ↑ plasma osmolality (3.5%) → triggers thirst and ADH release (renal H_2O retention)

> Pressure receptors are less sensitive BUT more potent than osmoreceptors → thus net effect is inhibit ADH secretion (net H_2O excretion), albeit LESS than Na^+ excretion → helps to ↓ plasma osmolality

- Effects on the body (including potential hazards) include:
  - (1) Cerebral effects
    - ↓ ICV and raised ICP → mannitol cannot cross BBB and effectively creates an osmotic gradient that draws EC brain fluid intravascularly → causes (i) Cerebral cell dehydration and (ii) ↓ CSF volume
    - CBF is preserved (assuming intact autoregulation)

        - Issues – (i) Cerebral oedema can worsen → if damaged BBB (Ie. mannitol enters brain), (ii) Repeat mannitol infusion causes rebound IC HTN (Ie. mannitol enters brain), (iii) NOT definitely therapy for ↑ ICP (cf. surgery)
    - (2) Renal effects
        - Causes diuresis due to:
            - (i) Osmotic diuresis → mannitol is freely filtered by glomerulus and neither secreted nor reabsorbed by tubules → osmotically active solute retains H_2O/electrolytes in urine
            - (ii) Pressure diuresis → due to ↑ RBF (a/w ↑ ECFV)
        - Beneficial in preventing tubular obstruction (Ie. due to myoglobin), maintaining renal function (Ie. during vascular surgery), and initiating diuresis with renal transplant
        - Issues – (i) Excess H_2O/solute loss (esp Na^+) → hypovolaemia/electrolyte (↓ Na^+/K^+) imbalance, (ii) Disruption of medullary interstitial gradient → lose urine concentrating ability
    - (3) Fluid/electrolyte imbalance
        - Tissue dehydrating effect (Ie. fluid shift into IV space) → hypervolaemia (Ie. volume overload, HTN, CCF), ↓ plasma osmolality and ↓ Na^+/K^+
        - Diuresis → hypovolaemia (Ie. hypotension, organ hypoperfusion), ↑ plasma osmolality (> 320 mosm/L), ↑ Na^+/K^+ (esp with > 3 g/kg/day)
    - (4) Other effects:
        - (i) Haemodilution (2° to hypervolaemia → ↓ Hcrt) → improves blood flow/O_2 delivery to tissues
        - (ii) ↓ IOP (similar to ICP)
        - (iii) Cell protection (as a free radical scavenger)
        - (iv) Tissue/vein irritant (due to hypertonicity)
        - (v) Allergic reactions (rare)

Body handling of 1000 mL 3% saline:

- ↑ Na^+ content effectively limits distribution to ECF compartment
- It is hyperosmolar cf plasma (1027 mosm/L vs 290 mosm/L) → hypertonicity causes H_2O shift from ICF to ECF → ↑ ECFV while ↓ ICFV
- Effect of 1000 mL infusion of 3% saline:

Pre infusion:
- TBW = 42 L
- Total body solute = 42 L x 290 = 12180 mosm
- ECF solute = 14 L x 290 = 4060 mosm
- ICF solute = 28 L x 290 = 8120 mosm

Post-infusion:
- TBW = 42 L + 1 L = 43 L
- Total body solute = 12180 + 1027 = 13207 mosm
- ECF solute = 4060 + 1027 = 5087 mosm
- ICF solute = 8120 mosm (same)

So:
- Plasma osmolarity = 13207 mosm/43 L = 307 mosm/L
- ECFV = 5087 mosm/307 mosm/L = 16.6 L
- ICFV = 8120 mosm/307 mosm/L = 26.5 L

- Net effect is:
    - ↓ ICFV by 1.5 L → affects brain cells (dehydration → confusion/obtundation)
    - ↑ ECFV by 2.6 L → 2L in ISF and 0.5L in PV
        - ↑ ISFV does not cause oedema → handled by lymphatic system
        - ↑ BV by 10% → triggers BRR → (i) Inhibits ADH secretion → renal H_2O excretion, and (ii) Stimulates ANP release and inhibits RAAS → natriuresis and diuresis (lose Na^+/H_2O)
    - ↑ plasma osmolality (5%) → triggers thirst and ADH release (renal H_2O retention)

> Note → Pressure receptors are less sensitive BUT more potent than osmoreceptors → thus net effect is inhibit ADH secretion (net H_2O excretion), albeit LESS than Na^+ excretion → helps to ↓ plasma osmolality

Body handling of 100 mL 8.4% $NaHCO_3$:

- (1) Effect of addition of alkali load (due to HCO_3^-):
  - (a) Acute metabolic alkalosis
    - ↑ ECF [HCO_3^-] due to administration of exogenous HCO_3^- → moreover, Na^+ in the solution will restrict HCO_3^- distribution to ECF → lead to an acute metabolic alkalosis
    - Normally, if plasma HCO_3^- > 27 mmol/L → HCO_3^- will be rapidly excreted in urine and acute metabolic alkalosis should rapidly self-correct (unless there is underlying pathology to maintain it, such as acidosis due to cardiac arrest)
  - (b) ↓ ECF K^+ – ↑ ECF [HCO_3^-] due to exogenous administration of a base will cause an intracellular shift of EC K^+ → useful in treating hyperkalaemia during emergencies (Ie. cardiac arrest)
  - (c) ↑ CO_2 load – Addition of exogenous HCO_3^- will ↑ reassociation of HCO_3^- with H^+ to form H_2CO_3 → ↑ CO_2 load → this is exacerbated during asystolic arrest due to lack of cardiac output (↓ CO_2 excreted by lungs)
  - (d) Intracellular acidosis – CO_2 diffuses intracellular and is hydrated to form H_2CO_3, which then dissociates to form H^+ → this is exacerbated during asystolic arrest due to lack of cardiac output (↑ CO_2 diffuses into cell)
  - (e) Effect on respiratory control → ↑ minute ventilation due to ↑ CO_2 load
  - (f) Right shift in O_2 Hb dissociation curve → due to Bohr effect 2° to ↑ CO2 load
- (2) Addition of a salt load (due to Na^+):
  - Solution's Na^+ content limits the distribution of fluids only to the ECF
  - ↑ ECF [Na^+] → degree of ↑ will depend on (i) the amount of solution given, and (ii) the degree of EC shift of IC H_2O due to osmosis (2° to ↑ plasma osmolality)
  - Useful in treating acute hyponatraemia
- (3) Addition of a hypertonic load (2000 mosm/L x 100 mL = 200 mosm):

Pre-infusion:
- TBW = 42 L
- Total body solute = 42L x 290 = 12180 mosm
- ECF solute = 14L x 290 = 4060 mosm
- ICF solute = 28L x 290 = 8120 mosm

Post-infusion:
- TBW = 42 L + 0.1 L = 42.1 L
- Total body solute = 12180 + 200 = 12380 mosm
- ECF solute = 4060 + 200 = 4260 mosm
- ICF solute = 8120 mosm (same)

So:
- Plasma osmolarity = 12380 mosm/42.1 L = 294 mosm/L
- ECFV = 4260 mosm/294 mosm/L = 14.5 L
- ICFV = 8120 mosm/294 mosm/L = 27.6 L

  - Net effects are:
    - (i) ↓ ICFV by 400 mL → minimal cellular effect
    - (ii) ↑ ECFV by 500 mL (375 mL ISF + 125 mL PV) → ↑ is greater than volume of solution delivered to it → due to the extracellular shift of IC H_2O 2° to osmosis
      - ↑ ISFV does not cause oedema → handled by lymphatic system
      - ↑ BV by 2.5% only → does not trigger BRR
    - (iii) ↑ plasma osmolality (1.3%) → triggers thirst and ADH release (renal H_2O retention)
    - (iv) ↑ urine production 2° to ↑ ECFV → ↑ ECFV will ↓ plasma $P_{ONCOTIC}$ → lead to ↑ GFR and slight ↓ PCT H_2O reabsorption due to glomerulotubular imbalance → larger ↑ in urine flow and excretion of injected fluid

Body handling of 100 mL 1 N HCl:

- Used for chronic respiratory acidosis with ↑ plasma $[HCO_3^-]$ → to normalise $[HCO_3^-]$
- 100 mL 1N HCl → 100 mmol H^+ load causes metabolic acidosis → this is prevented by:
    - (1) Buffering (immediate)
        - Rapid titration of H^+ against EC buffers (esp HCO_3^-):

$$\text{ECF } HCO_3^- \text{ pool} = [HCO_3^-] \times \text{ECFV} = 24 \text{ mmol/L} \times 14 \text{ L} = 336 \text{ mmol}$$

$$[HCO_3^-] \text{ post-buffering} = 24 \text{ mmol/L} \times (336\text{-}100 \text{ mmol})/336 \text{ mmol}$$
$$= 16.8 \text{ mmol/L (assuming all } H^+ \text{ is buffered by } HCO_3^- \text{ system)}$$

    - (2) Respiratory compensation (hrs-days)
        - Acidosis stimulates peripheral chemoreceptors → ↑ MV → ↓ $PaCO_2$ to normalise pH
        - Compensation starts early but takes 12-24 hrs for full effect → because:
            - Initial ↓ $PaCO_2$ causes ↓ brain ECF CO_2 → ↓ $[H^+]$ around central chemoreceptors in medulla → this inhibits any further ↑ MV
            - But HCO_3^- slowly equilibrates across BBB → gradual ↓ brain ECF $[HCO_3^-]$ and ↑ $[H^+]$ → removes inhibition on ventilation → further compensation of acidosis by ↑ MV
        - Note → partial compensation only:

$$\text{Expected } PCO_2 = 1.5 \times [HCO_3^-] + 8$$

    - (3) Renal correction (days)
        - Renal excretion of excess acid anion (Cl^-)→ equivalent to excretion of H^+ and reabsorption of HCO_3^- → eventual restoration of acid-base status
- Physiological effects of metabolic acidosis from 100 mL 1N HCl:
    - (1) Shift in Hb O_2 dissociation curve:
        - Right shift due to acidosis → ↓ O_2 affinity (Ie. assisting peripheral O_2 delivery)
        - Left shift due to ↓ 2,3-DPG synthesis (2° to acidosis) → ↑ O_2 affinity (Ie. assisting O_2 loading in the lungs)
    - (2) Normal anion gap → hyperchloraemic metabolic acidosis
    - (3) Hyperkalaemia → cell membrane H^+/K^+ exchanger extrudes IC K^+ for EC H^+ → this leads to net urinary K^+ losses
    - (4) Hypocapnoea (as part of compensatory response) → causes IC alkalosis → depresses cellular activity