Local Anesthetic Systemic Toxicity
LAST

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Objectives

At the conclusion of this presentation, the participant will be able to:

- Identify factors that place a patient at risk for LAST.
- Identify the treatment for cardiac arrest with LAST
- Recognize the dosage of lipid emulsion in the treatment of LAST.
- Identify the unique differences and precautions with liposomal bupivacaine.

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Local Anesthetics

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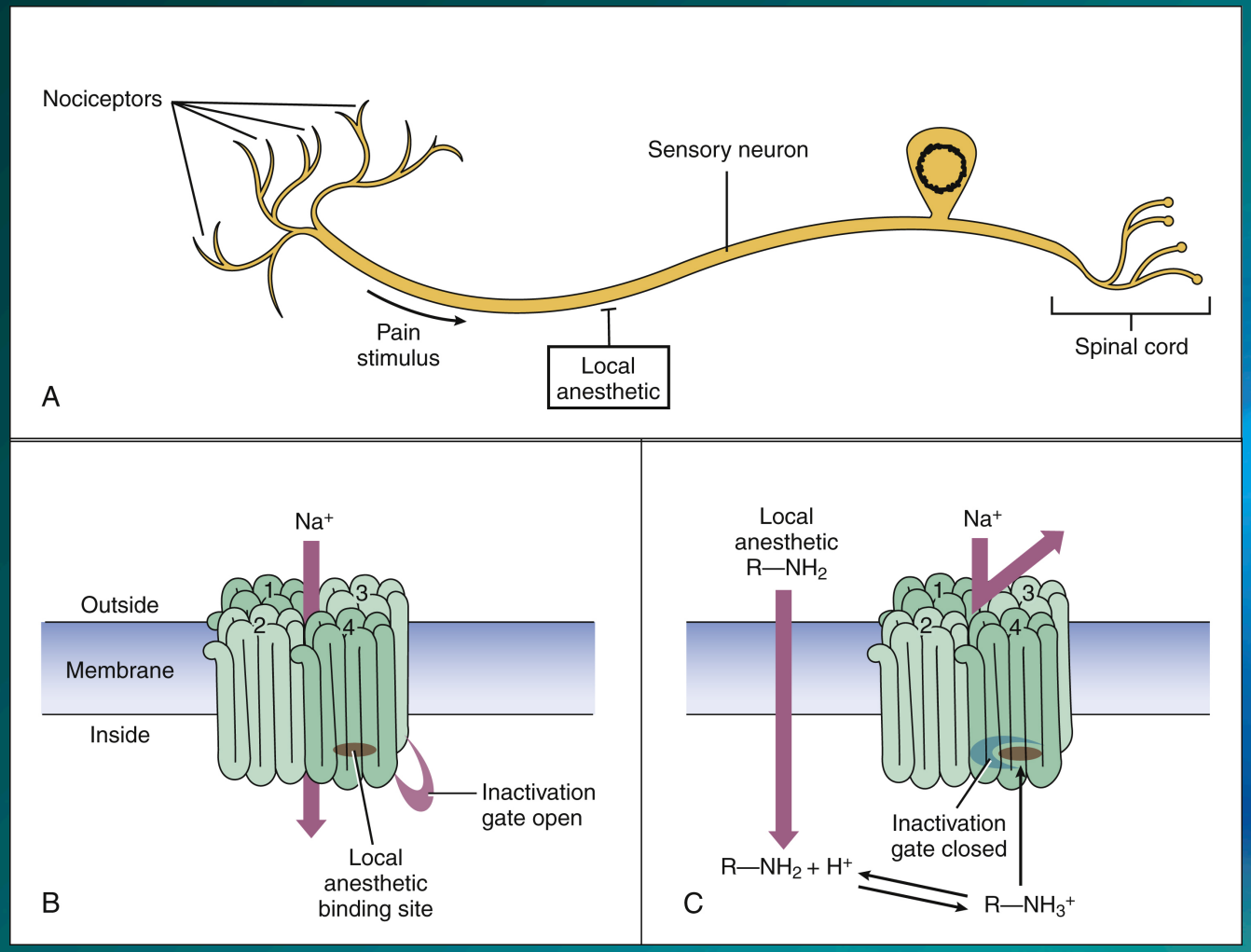
Local Anesthetics



- Reversibly blocks the conduction of electrical impulses at the sodium channels
  - ANS Blockade
  - Sensory Blockade
  - Motor Blockade

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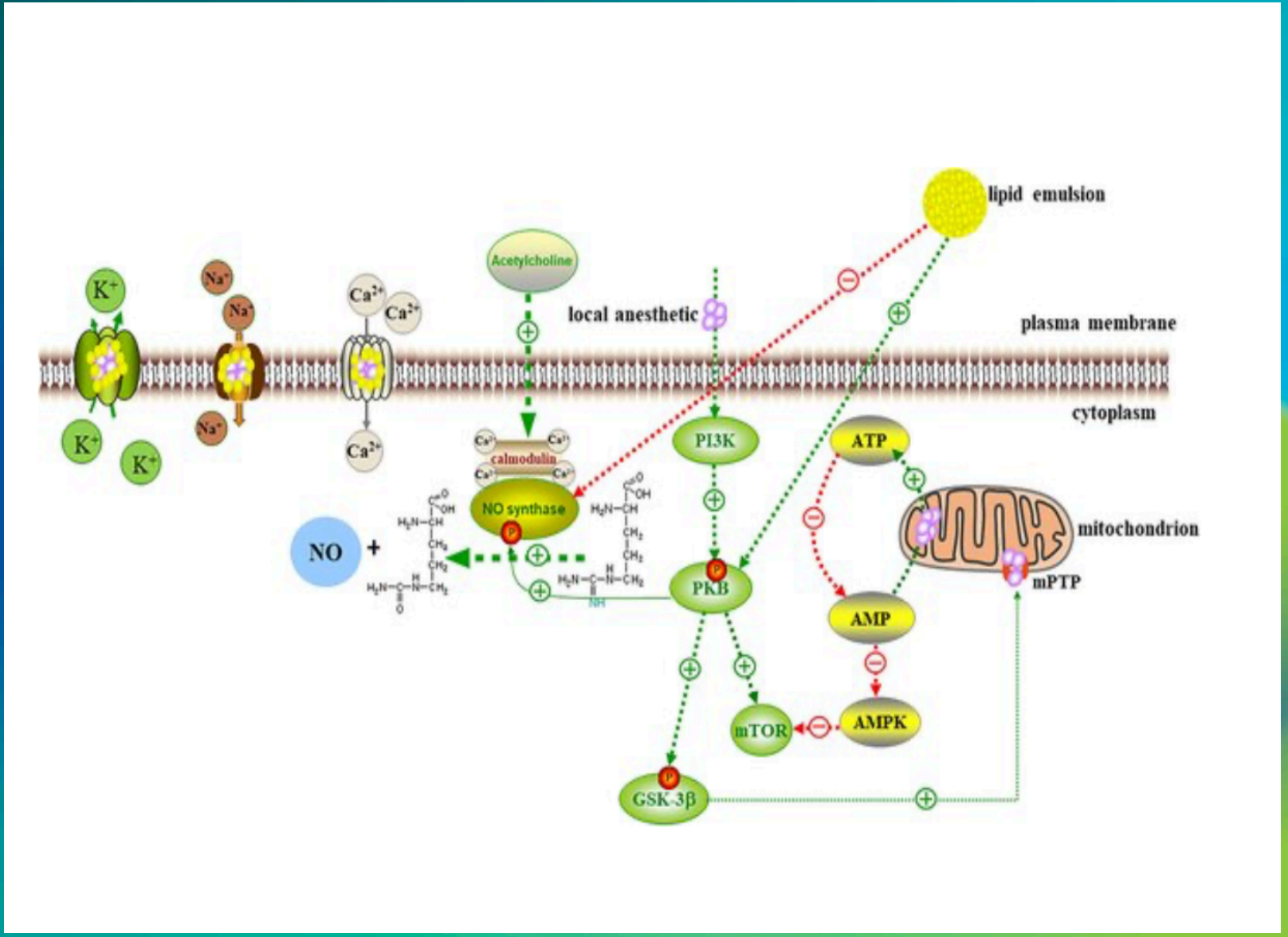
Local Anesthetics

- Also blocks calcium channels
- Na-K ATPase channels
- Block protein kinase signaling induced by TNF alpha
- Inhibits carnitine-acycarnitine translocation in the mitochrondria



Local Anesthetic Systemic Toxicity
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Incidence- 1 per 1,000 nerve blocks

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- Due to excess plasma concentration of the local anesthetic
  - Direct intravascular injection
  - Absorption from the injection site
    - Dose
      - Large volumes
      - Continuous infusions
    - Vascularity of the tissues
    - Addition of Epinephrine

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Highest Serum Levels

- Site of injection
  - Intercostal nerve blocks/PVB
  - Epidural/caudal (0.1/1000)
  - Brachial plexus block
  - LE blocks
    - Femoral/Sciatic nerve blocks
  - Subcutaneous

Vulnerable Patients

- Hypoxia and acidosis
- Underlying heart disease
- Extremes of age
- Fraility
- Small patient size or muscle mass
- Underlying hepatic, neurologic or metabolic co-morbidities Mitochondrial dysfunction (carnitine deficiency)
- Renal dysfunction
- Pregnancy

EXTREME VIGILANCE FOR THOSE AT RISK

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Use of Ultrasound & LAST

- Studies show major cases of LAST (seizures, cardiac arrest) has decreased by 2/3rds
  - 10 cases per 10,000 down to 2.6 cases per 10,000
- Most cases of LAST before ultrasound occurred within the first minutes
  - U/S decreases incidence of immediate LAST
- Now occurs later often 10 minutes after the block
  - Monitoring for 30 minutes after the block
- 16% despite U/S

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Settings

- 80%- Hospitals
- 10%- Offices
- 10%- ER, Home

- Anesthesia providers- 60%
- Surgeons- 30%
- 10%-
  - Dentists
  - Emergency physicians
  - Cardiologists
  - Pediatricians
  - Dermatologists

- 44%-Lidocaine
- 22%- Lidocaine and another LA
- 11%- Bupivacaine
- 11%- Ropivacaine

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Sites

- Epidural and caudal- 15%
- Extremity blocks- 20%
- Penile blocks-20%
- Local Infiltration- 20%
- Other:
  - Continuous IV infusion
  - PVB
  - Peribulbar
  - TAP
  - Maxillary nerve blocks
  - Oral, esophageal, tracheal mucosal application

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LAST Presentation

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Central Nervous System

- Initially- 16%-30%
  - Numbness of the tongue/circumoral tissues- metallic taste
  - Facial tingling
  - Restlessness/Agitation/Drowsiness
  - Vertigo
  - Tinnitus
  - Difficulty in focusing- visual auditory disturbances
- Slurred speech
- Skeletal muscle twitching
  - Initially face and extremities
- Tonic/Clonic Seizures (50%)
- Loss of consciousness/Coma

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Cardiovascular System

- 24% isolated CV effects
- Tachycardia and Hypertension
- Hypotension
- Cardiac dysrhythmias
  - AV blocks, Idioventricular rhythms
  - VT/VF
- Threshold may be decreased by beta blockers, digitalis, and calcium channel blockers
- Depressed myocardial contractility →hypotension, bradycardia, asystole
- Bupivacaine- Binds more avidly and longer to cardiac sodium channels

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Lipid Emulsion for LAST

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History

- 1998- Guy Weinberg MD
- Typical scenario
  - Witnessed
  - Failed to recover with epi, vasopressin, or antiarrythmics
  - ROSC after lipid emulsion infusion

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Presentation

- "Mild" LAST- 1:1,000 patients
- Seizures- 0-25: 10,000 patients
- CV Instability/Cardiac Arrest- Smaller fraction of patients
- Classic Textbook- <40% of Patients
  - Seizure
  - Cardiac Arrest
  - 5-30 minutes after injection
- Used early→ attenuation or prevention of progression to cardiac toxicity

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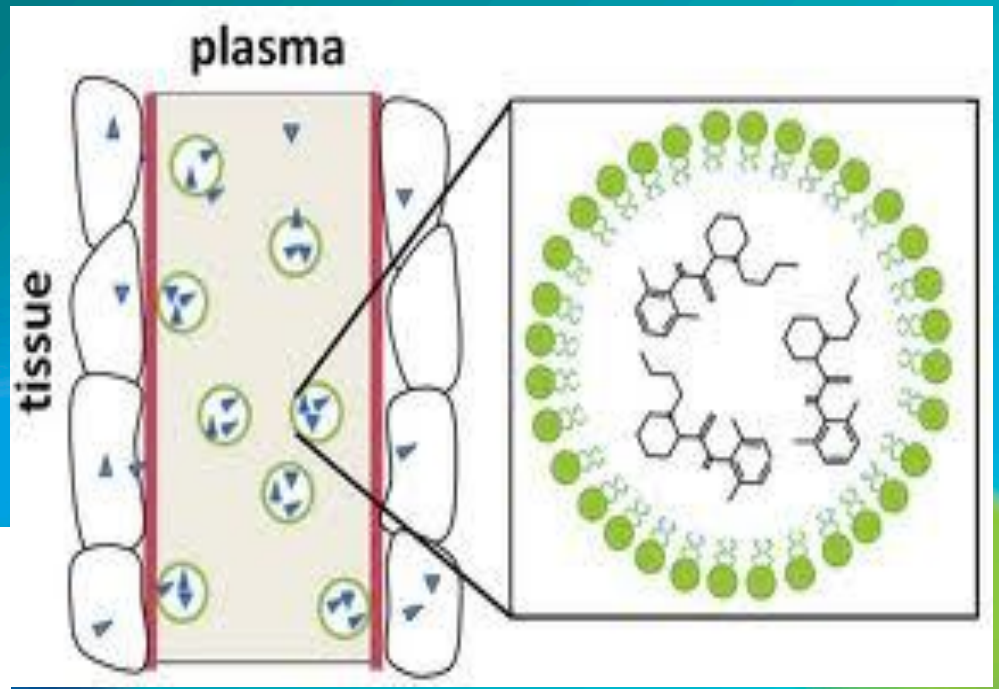
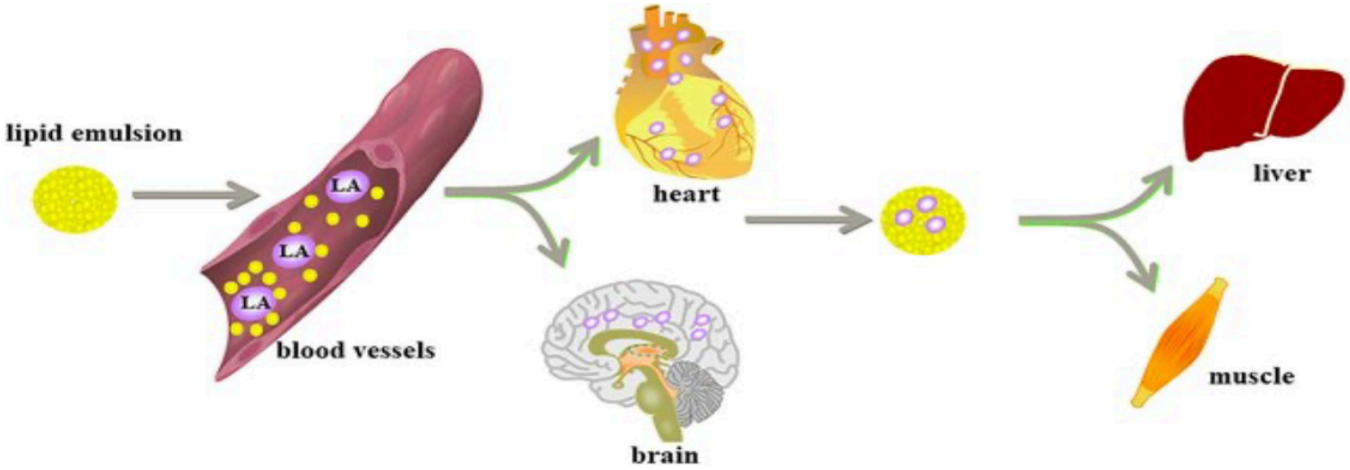
Mechanisms of Action

- Lipid Sink
  - Expands the lipid plasma compartment- temporarily
  - Pulls the lipophilic drugs
- Lipid Shuttle/Subway
  - Scavenges the LA and redistributes it





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Mechanism of Action

- Lipid Flux- Metabolism
  - Energy source for the myocardium
  - Cardiotonic effects
- Activation of calcium channels
  - Maintain calcium concentrations
  - Maintain coronary perfusion pressure
  - Increase ATP in mitochondria

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ASRA Guidelines

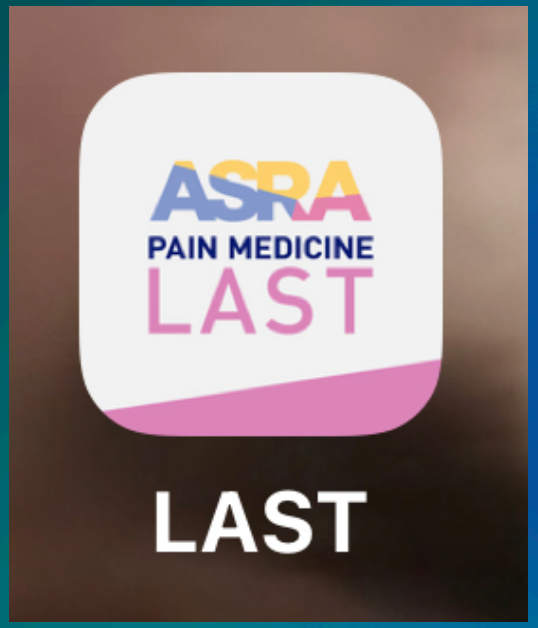
The Pharmacologic Treatment of LAST is Different from Other Cardiac Arrest Scenarios

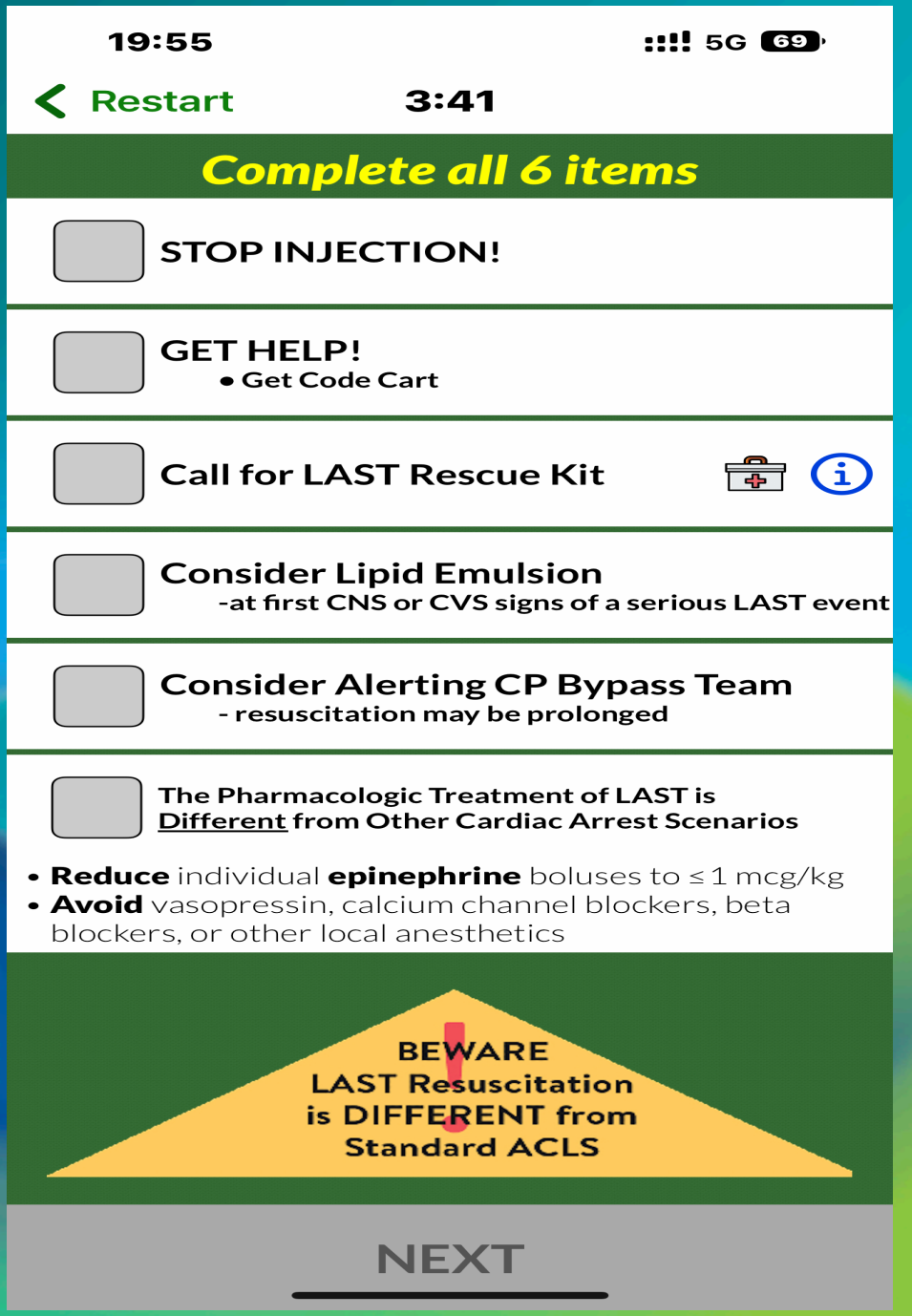
- **Reduce** individual **epinephrine** boluses to ≤ 1 mcg/kg
- **Avoid** vasopressin, calcium channel blockers, beta blockers, or other local anesthetics

- Stop injecting local anesthetic
- Get help
  - Consider lipid emulsion therapy at the first sign of a serious LAST event
  - Call for the LAST Rescue Kit
  - Alert the nearest cardiopulmonary bypass team - resuscitation may be prolonged
- Airway management
  - Ventilate with 100% oxygen / avoid hyperventilation / advanced airway device if necessary
- Control seizures
  - Benzodiazepines preferred
  - **Avoid** large doses of **propofol**, especially in hemodynamically unstable patients
- Treat hypotension and bradycardia – **If pulseless, start CPR**

Lipid Emulsion 20% (Precise volume and flow rate are not crucial)	
Greater than 70 kg patient	Less than 70 kg patient
Bolus 100 mL Lipid Emulsion 20% rapidly over 2-3 minutes • Lipid emulsion infusion 200-250 mL over 15-20 minutes	**Bolus 1.5 mL/kg Lipid Emulsion 20%** rapidly over 2-3 minutes • Lipid emulsion infusion ~0.25 mL/kg/min (ideal body weight)
If patient remains unstable: • Re-bolus once or twice at the same dose and double infusion rate; be aware of dosing limit (12mL/kg) • Total volume of lipid emulsion can approach 1 L in a prolonged resuscitation (e.g., > 30 minutes)	

ASRA LAST App





Local Anesthetic Systemic Toxicity Checklist

ASRA

- Call for help
- Get LAST rescue kit
- Consider cardiopulmonary bypass team

+ Consider administering LIPID EMULSION early

LIPID EMULSION 20%

The order of administration (bolus or infusion) and method of infusion (manually, iv roller clamp, or pump) are not critical

over 70 kg

- Bolus ~100 mL over 2-3 min
- Infuse ~250 mL over 15-20 min

IF PATIENT REMAINS UNSTABLE:
- Repeat bolus
- Double infusion

under 70 kg

- Bolus ~1.5 mL/kg over 2-3 min
- Infuse ~0.25 mL/kg/min (consider using a pump if <40 kg)

IF PATIENT REMAINS UNSTABLE:
- Repeat bolus
- Double infusion

Seizure?

- Ensure adequate airway
- Benzodiazepine preferred
- If only propofol available, use low dose, e.g., 20 mg increments

Arrhythmia or Hypotension?

BEWARE
LAST Resuscitation is DIFFERENT from Standard ACLS

ASRA PAIN MEDICINE EDUCATION RESEARCH

EPINEPHRINE

- Smaller than normal dose preferred
- Start with ≤1 mcg/kg

AVOID

- Local anesthetics
- Beta-blockers
- Calcium channel blockers
- Vasopressin

Stable?

- Continue lipid emulsion ≥15 min once hemodynamically stable
- Maximum lipid dose: 12 mL/kg

Once Stable, OBSERVE

- 2 hrs after seizure
- 4-6 hrs after cardiovascular instability
- As appropriate after cardiac arrest

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IF PATIENT REMAINS UNSTABLE:

- Repeat bolus
- Double infusion

LipidRescue - Fat emulsion 20%

TOTAL Body Weight*	Load ¥	Infusion ¥
	Bolus over 1 minute (provides 1.5 mL/kg)	Infusion 0.25 ml/kg/min shown as INFUSION IN ML/HR
3 kg	4.5 mL	45 ml/hr
4 kg	6 mL	60 ml/hr
5 kg	7.5 mL	75 ml/hr
6 kg	9 mL	90 ml/hr
7 kg	10.5 mL	105 ml/hr
8 kg	12 mL	120 ml/hr
9 kg	13.5 mL	135 ml/hr
10 kg	15 mL	150 ml/hr
11 kg	16.5 mL	165 ml/hr
12 kg	18 mL	180 ml/hr
13 kg	19.5 mL	195 ml/hr
14 kg	21 mL	210 ml/hr
15 kg	22.5 mL	225 ml/hr
16 kg	24 mL	240 ml/hr
17 kg	25.5 mL	255 ml/hr
18 kg	27 mL	270 ml/hr
19 kg	28.5 mL	286 ml/hr
20 kg	30 mL	300 ml/hr
22 kg	33 mL	330 ml/hr
24 kg	36 mL	360 ml/hr
26 kg	39 mL	390 ml/hr
28 kg	42 mL	420 ml/hr
30 kg	45 mL	450 ml/hr
32 kg	48 mL	480 ml/hr
34 kg	51 mL	510 ml/hr
36 kg	54 mL	540 ml/hr
40 kg	60 mL	600 ml/hr
45 kg	67.5 mL	675 ml/hr
50 kg	75 mL	750 ml/hr
55 kg	82.5 ml	825 ml/hr
60 kg	90 ml	900 ml/hr
65 kg	97.5 ml	975 ml/hr

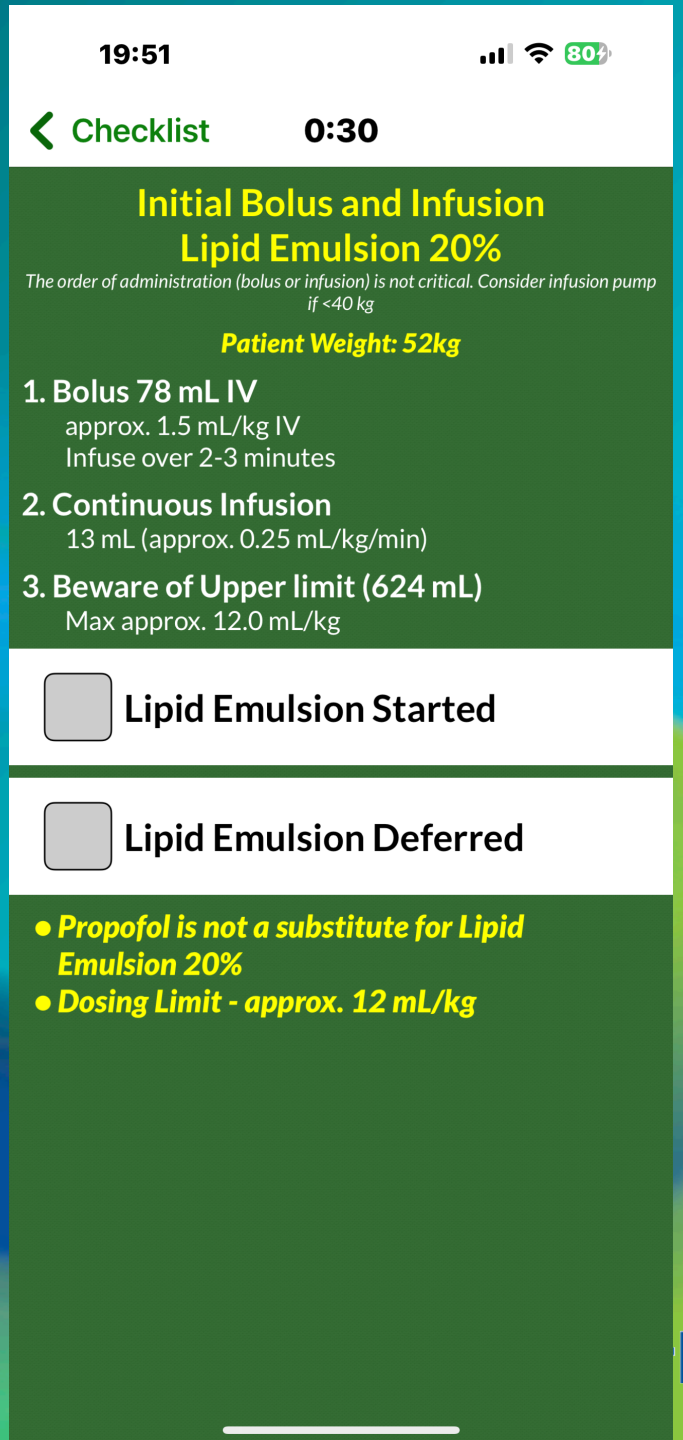
Utilize standard flat dosing for all patients >/= 70kg

For patients greater than or equal to 70 kg- Bolus 100 ml of Lipids followed by infusion of 250 ml over 20 minutes

¥ If patient remains unstable, rebolus once or twice at the same dose and double the infusion rate (may require #2 pumps). Call pharmacy if more 20% lipid bags required. Be aware of TOTAL dosing limit (12 mL/kg).

How to set BBraun Outlook 400 for INITIAL infusion setting for patients >/= 70 kg

1. Go to Alternative Menu setting
2. Go to Set Time and Volume mode
3. Set time to 20 minutes and volume 250 cc



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- Ensure adequate airway
- Benzodiazepine preferred
- If only propofol available, use low dose, e.g., 20 mg increments

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EPINEPHRINE

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- Start with ≤1 mcg/kg

AVOID

- Local anesthetics
- Beta-blockers
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- Vasopressin

Stable?

- Continue lipid emulsion ≥15 min once hemodynamically stable
- Maximum lipid dose: 12 mL/kg

Once Stable, OBSERVE

- 2 hrs after seizure
- 4-6 hrs after cardiovascular instability
- As appropriate after cardiac arrest

Graphic: Erin Jane

Epinephrine in Cardiac Arrest from LAST

- High dose Epi (>10 mcg/kg) → hyperlactic acidosis and inhibits the resuscitative effect of lipid emulsion
  - Increases arrhythmias
  - Lipids should be given priority before low dose epinephrine
  - Reduces LV pressures and diastolic dysfunction and reduces lung damage → improved survival

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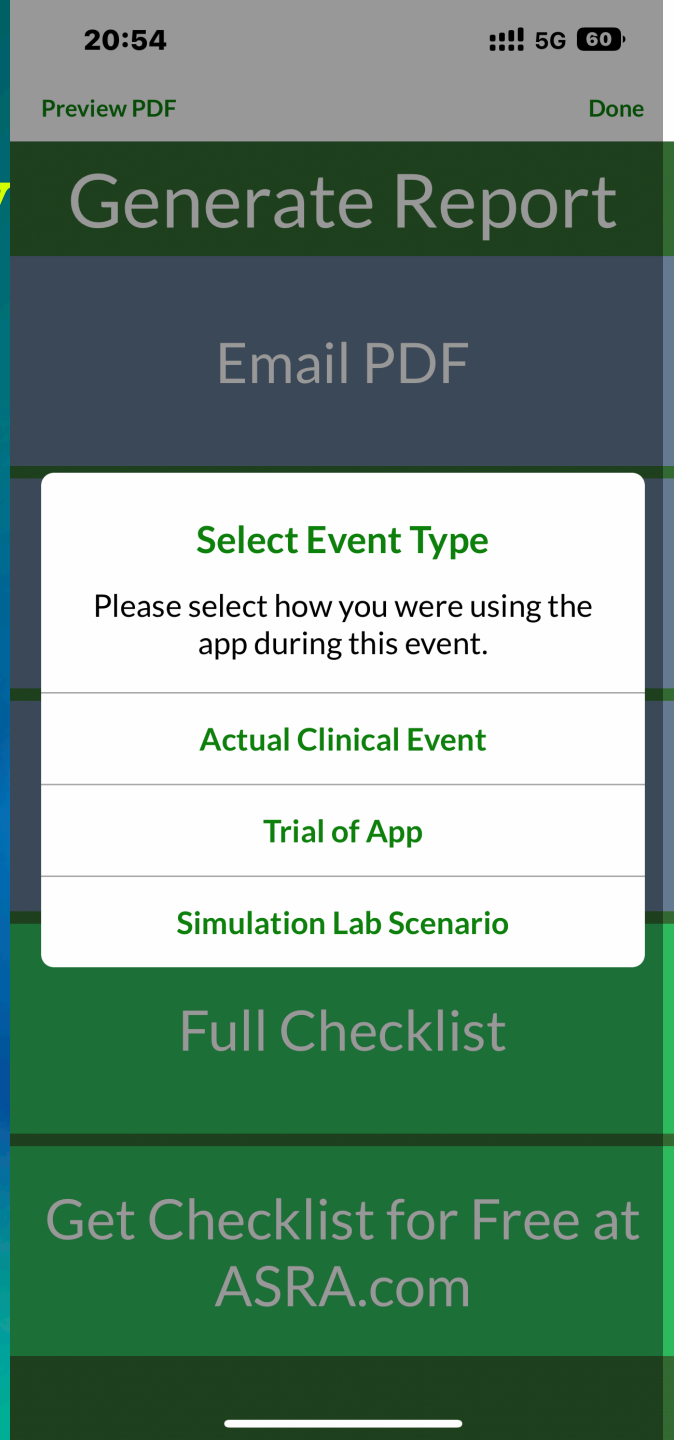
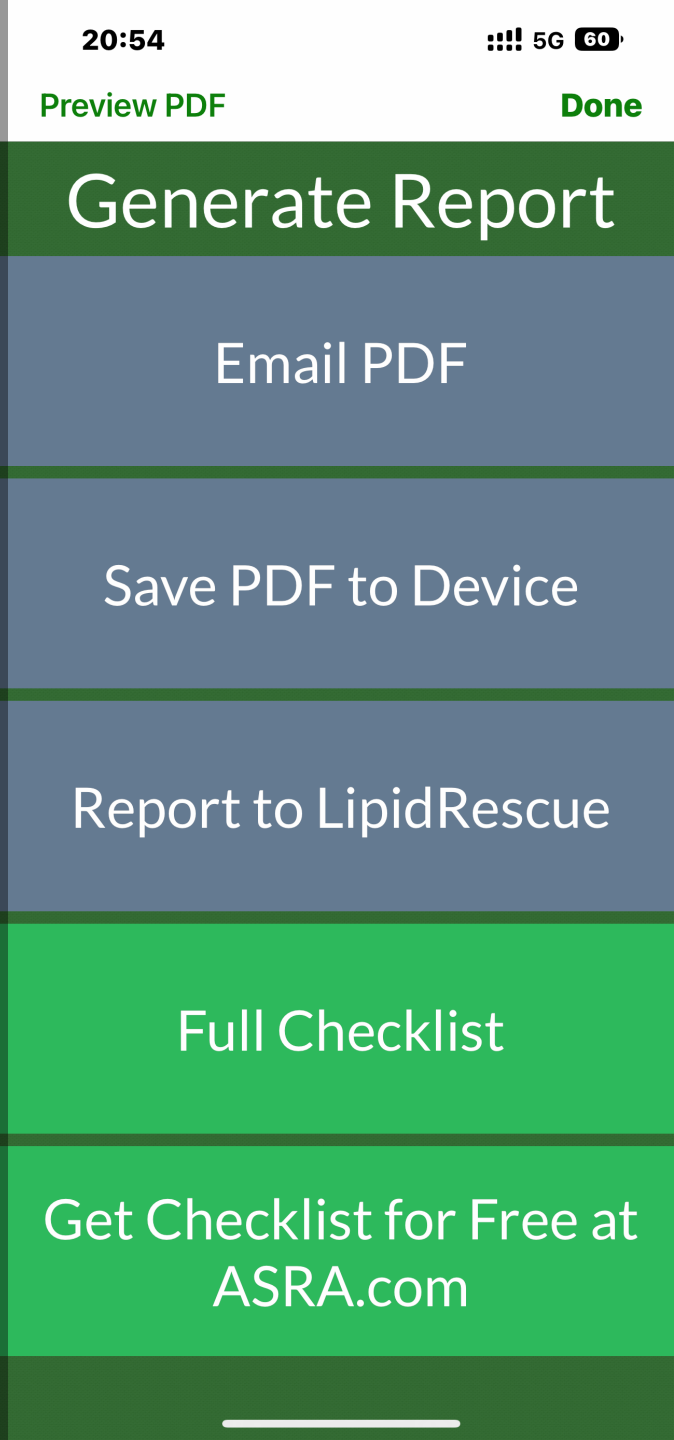
Monitoring After an Ev

- After neurological symptoms only: Observe for at least 2 hours
- If limited with no CV compromise and lipids given- observe for 30-40 minutes and may proceed with surgery if no recurrence
- After CV compromise: Observe for at least 4-6 hours
- Cardiac arrest- longer
- Report to national registries





Lipid Rescue Kit

- Lipids
  - (2) 250 cc bags OR
  - (1) 500 cc bag
- 60 cc syringes
- 2 Filtered IV Pump tubing
- Checklist
- Flowchart
- Infusion Rate List

1000 cc Lipids (ASRA)

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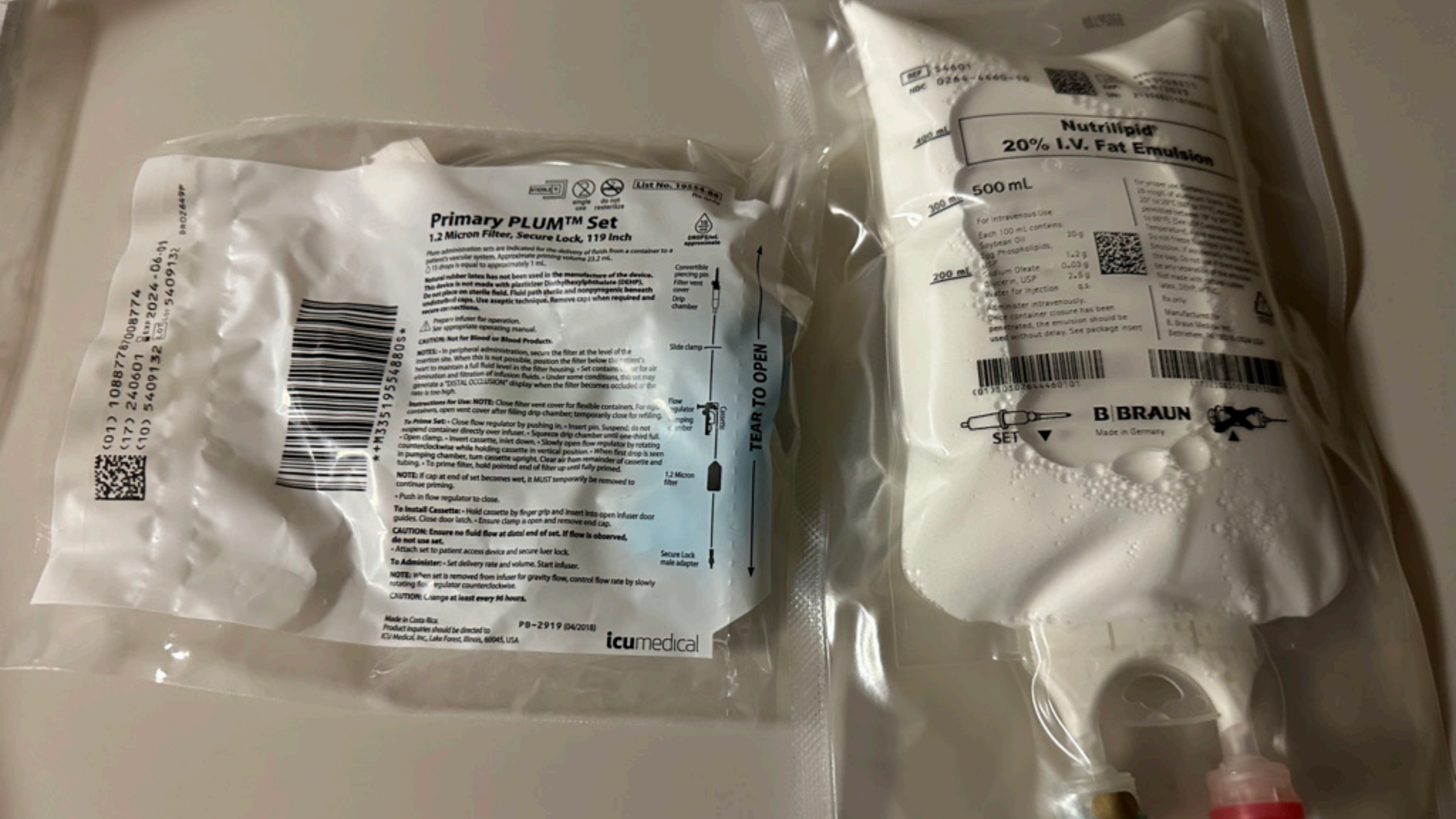

Primary PLUM™ Set
1.2 Micron Filter, Secure Lock, 119 Inch
List No. 19554-86
single use
do not resterilize
DROP(s)/mL approximate
Plum administration sets are indicated for the delivery of fluids from a container to a patient's vascular system. Approximate priming volume 23.2 mL.
15 drops is equal to approximately 1 mL.
Natural rubber latex has not been used in the manufacture of the device.
This device is not made with plasticizer Diethylhexylphthalate (DEHP).
Do not place on sterile field. Fluid path sterile and nonpyrogenic beneath undisturbed caps. Use aseptic technique. Remove caps when required and secure connections.
Prepare infuser for operation.
See appropriate operating manual.
CAUTION: Not for Blood or Blood Products.
NOTES: • In peripheral administration, secure the filter at the level of the insertion site. When this is not possible, position the filter below the patient's heart to maintain a full fluid level in the filter housing. • Set contains a filter for air elimination and filtration of infusion fluids. • Under some conditions, this set may generate a "DISTAL OCCLUSION" display when the filter becomes occluded or the rate is too high.
Instructions for Use: NOTE: Close filter vent cover for flexible containers. For rigid containers, open vent cover after filling drip chamber; temporarily close for refilling.
To Prime Set: • Close flow regulator by pushing in. • Insert pin. Suspend; do not suspend container directly over infuser. • Squeeze drip chamber until one-third full. • Open clamp. • Invert cassette, inlet down. • Slowly open flow regulator by rotating counterclockwise while holding cassette in vertical position. • When first drop is seen in pumping chamber, turn cassette upright. Clear air from remainder of cassette and tubing. • To prime filter, hold pointed end of filter up until fully primed.
NOTE: If cap at end of set becomes wet, it MUST temporarily be removed to continue priming.
• Push in flow regulator to close.
To Install Cassette: • Hold cassette by finger grip and insert into open infuser door guides. Close door latch. • Ensure clamp is open and remove end cap.
CAUTION: Ensure no fluid flow at distal end of set. If flow is observed, do not use set.
• Attach set to patient access device and secure luer lock.
To Administer: • Set delivery rate and volume. Start infuser.
NOTE: When set is removed from infuser for gravity flow, control flow rate by slowly rotating flow regulator counterclockwise.
CAUTION: Change at least every 96 hours.
Convertible piercing pin
Filter vent cover
Drip chamber
Slide clamp
Flow regulator
Pumping chamber
1.2 Micron filter
Secure Lock male adapter
TEAR TO OPEN
Made in Costa Rica.
Product inquiries should be directed to ICU Medical, Inc., Lake Forest, Illinois, 60045, USA
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Nutrilipid®
20% I.V. Fat Emulsion
500 mL
400 mL
300 mL
200 mL
For Intravenous Use
Each 100 mL contains:
Soybean Oil, USP 20 g
Egg Phosphatides, NF 1.2 g
Sodium Oleate, USP 0.03 g
Glycerin, USP 2.5 g
Water for Injection q.s.
Administer intravenously.
Once container closure has been penetrated, the emulsion should be used without delay. See package insert.
Rx only
Manufactured for B. Braun Medical Inc. Bethlehem, PA
(01)10302644460101
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B BRAUN
Made in Germany

Lipid Rescue

- Used to Treat Toxicity from lipophilic drugs
  - Calcium channel blockers
  - Beta blockers
  - Haldol
  - Antimalarial drugs
  - Organophosphates
  - Others

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Prevention

- Assessing patient risk factors
- Use of ultrasound
- Less toxic drugs
- Use of a vascular marker (epi)
- Adequate monitoring
- Incremental injection (3-5 ml)
- Intermittent aspiration
- Individualized dosing
- System safety and preparedness
- Use of lowest effective dose

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Local Anesthetic Maximum Doses

Local Anesthetic	Max Dose Plain mg/kg (With Epi)
Bupivacaine	2.5 (3 with Epi)
Lidocaine	4.5 (7 with Epi)
Mepivacaine	4.5 (7 with Epi)
Prilocaine	7
Ropivacaine	3 (3.5 with Epi)
Cocaine	3
Chloroprocaine	12
Procaine	2
Tetracaine	3

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Dexmedetomidine

- Reduces spinal cord neurotoxicity caused by lidocaine
  - Inhibits glutamate release
  - Inhibits protein-kinase C pathways
  - Mechanism similar to how lipids work
- Reduces cardiotoxicity but unclear mechanism
  - More research

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Liposomal Bupivacaine- Exparel

- LA in nanoparticle carrier mix
  - 266 mg (1.3%) bupivacaine
  - 3% of the drug is free
  - 96 hrs
  - Can only mix with bupivacaine but in not > 1:2
- Can administer 20 minutes after Lidocaine IV or to same site
- Approved for infiltration techniques and interscalene blocks
- Increased relationship between LAST and Exparel in some studies
- No other LA for 96 hours

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QUESTIONS