Critical Updates in the ICU

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Disclosures

- I have no actual or potential conflicts of interest in relation to this presentation.

TOC

- TTM/therapeutic hypothermia.
- Steroids in sepsis, ARDS, CAP.
- Glycemic control in critically ill adults.
- ADA DKA 2024 update.

Clinical case #1

HPI: 48 year old male presents to ED via EMS with witnessed out-of-hospital cardiac arrest. Patient is homeless and was found amongst drug paraphernalia.

- Initial rhythm pulseless VT, defibrillated x 2.
- ROSC achieved in the field after 15 minutes of ACLS.

- Patient remains comatose and is intubated in ED for airway protection.
  - TnI 6 ng/mL; 12-lead ECG with sinus tachycardia; UDS positive for amphetamine.
  - Temperature 37 C.

Clinical case #1 – con't

- Post-ROSC care initiated, patient admitted to ICU.
  - Cardiology consultation obtained, LHC performed, no intervention.
- Family members ask…
  - "Are you going to pack him with ice to cool him down and help him survive?"
- Your response…

  A.) I've already placed the ArcticSun™ 5000 catheter and we're actively cooling to 36 C to improve neurologic outcome per our TTM policy.

  B.) We've placed ice packs, cooling fans, and are administering cold saline IV to achieve therapeutic hypothermia at 34 C to improve functional outcome.

  C.) We're not planning to actively cool but will treat fever if it occurs.

Therapeutic hypothermia - history

- Therapeutic hypothermia:
  - 2002 – Mild Therapeutic Hypothermia to Improve Neurologic Outcome after Cardiac Arrest (n=273).
    - Patients resuscitated after cardiac arrest due to ventricular fibrillation cooled to 32-34°C for 24 hours.
    - IC – witnessed arrest, VF or VT as initial rhythm, “cardiac origin of arrest”, 5-15 minutes from arrest to first attempt at CPR, and total code duration < 60 minutes to ROSC.
    - Primary end point – “favorable neurologic outcome” within six months.
    - Secondary end point(s) – mortality within six months, complications by 7 days.
  - 55% vs 39% met primary end point.
  - 41% vs 55% mortality.

Therapeutic hypothermia - history

- Therapeutic hypothermia:
  - 2002 – Treatment of Comatose Survivors of Out-of-Hospital Cardiac Arrest with Induced Hypothermia (n=77).
    - Patients cooled to 33°C for 12 hours.
    - IC – witnessed OOH arrest with ROSC and persistent coma </= 2 hours.
    - Primary outcome measure – “survival to hospital discharge with sufficiently good neurologic function to be discharged to home or a rehabilitation facility”.
  - 49 vs 26% met primary endpoint.

Therapeutic hypothermia versus TTM

- 2013 – TTM trial (n=939).
  - Patients divided into two groups, 33 vs 36°C, temperature maintained for 36 hours with rewarming beginning at 28 hours and maintained euthermia (no fever) for 72 hours post-arrest.
    - IC – witnessed OOH arrest of presumed cardiac origin with persistent ROSC and GCS < 8.
    - Primary end point of all-cause mortality by the end of the study.
    - Secondary outcome measures of neurologic outcome, Rankin scale score, and all-cause mortality by 6 months.
  - No difference in any end-point.
  - Complications more likely in 33°C group.

TTM/therapeutic hypothermia - history

- Takeaway – both studies demonstrated statistically significant improvements in neurologic outcome and survival.
    - IN patients with WITNESSED out-of-hospital cardiac arrest AND an initial SHOCKABLE rhythm who are PERSISTENTLY COMATOSE.
  - Broadly adopted to include all cardiac arrest patients everywhere with any rhythm, TTM study generally caused institutional switch to TTM rather than TH.
- 2015 – ILCOR guideline published (International Liaison Committee on Resuscitation):
  - ILCOR recommends TTM for adults with OOH cardiac arrest and an initial shockable rhythm at a constant temperature between 32 and 36°C for at least 24 hours.
    - “Suggestion” for OOH arrest with non-shockable rhythm and in-hospital cardiac arrest.

TTM/therapeutic hypothermia - history

- Subsequent evidence…
- 2019 - HYPERION (n=584).
  - OOH arrest with initial nonshockable rhythm cooled to 33°C for 24 hours.
  - Improved neurologic outcome (10% vs 5.7% with CPC 1-2), no difference in mortality.
- 2019 – PRINCESS (n=677).
  - Intra-arrest cooling and TH at 32-34°C for 24 hours.
  - No statistically significant difference in survival/neurologic outcomes.

TTM/therapeutic hypothermia - history

- 2021 - Targeted Temperature Management 2 Trial (n=1900).
  - Intervention group patients were immediately cooled to 33°C, maintained for 28 hours, then rewarmed to 37°C; normothermia was then maintained for 72 hours.
  - Control group – maintain temperature of 37.5°C or less (no active warming, APAP or TTM devices used if exceeded temperature goal).
  - IC – Witnessed OOH cardiac arrest of presumed cardiac (or unknown) etiology regardless of rhythm who were unconscious and unable to follow verbal commands with no verbal response to pain.
- Primary outcome – death from any cause at 6 months.
  - No difference.
- Secondary outcome – poor functional outcome at 6 months.
  - No difference.

TTM/TH – 2023 AHA Focused Update

- TEMPERATURE CONTROL
  - “We recommend all adults who do not follow commands after ROSC, irrespective of arrest location or presenting rhythm, receive treatment that includes a deliberate strategy for temperature control”.

Performance of Temperature Control		
COR	**LOE**	**Recommendations**
1	B-R	1. We recommend selecting and maintaining a constant temperature between 32°C and 37.5°C during postarrest temperature control.
1	B-NR	2. We recommend hospitals develop protocols for postarrest temperature control.
2a	B-NR	3. It is reasonable that temperature control be maintained for at least 24 h after achieving target temperature.
2b	B-NR	4. There is insufficient evidence to recommend a specific therapeutic temperature for different subgroups of cardiac arrest patients.
2b	C-LD	5. It may be reasonable to actively prevent fever in patients unresponsive to verbal commands after initial temperature control.
2b	C-EO	6. Patients with spontaneous hypothermia after ROSC unresponsive to verbal commands should not routinely be actively or passively rewarmed faster than 0.5°C per hour.
2b	B-R	7. The benefit of strategies other than rapid infusion of cold intravenous fluids for prehospital cooling is unclear.
3: No Benefit	B-R	8. We do not recommend the routine use of rapid infusion of cold intravenous fluids for prehospital cooling of patients after ROSC.

WHAT DOES IT MEAN?

- AHA update effectively gives us (as institutions) license to simply maintain euthermia in post-cardiac arrest patients.

Clinical case #2

HPI: 78 year old female admitted for severe CAP found unresponsive and pulseless in her room. CODE BLUE called/ACLS initiated immediately.

- Initial rhythm PEA.
- ROSC achieved after two rounds of ACLS/airway establishment.

- ABG – pH 6.8, $PaCO_2$ > 120 mmHg, PaO_2 53 mmHg, SaO_2 88%.
- 12-lead ECG – atrial fibrillation with rapid ventricular response.
  - T 39 C; BP 95/50 with norepinephrine at 0.2 mcg/kg/min.

Clinical case #2 – con’t

- Post-intubation ABG Ph 7.28, $PaCO_2$ 80 mmHg, PaO_2 95 mmHg, SpO_2 100%.
- Patient localizes to pain but does not open eyes or interact.
- Next steps?
  - Continue to manage underlying precipitants.
  - Treat fever.

Clinical scenario #3

HPI: 54 year old obese male with no other significant history is brought to ED via EMS after being intubated in the field. Initial complaint of dyspnea, patient was severely hypoxemic, labored, and poorly responsive on assessment.

- Nasal swab positive for Influenza A; MRSA PCR positive.
- CXR demonstrates extensive bilateral airspace disease.
- ABG with pH 7.25, $PaCO_2$ 65 mmHg, PaO_2 58 mmHg, and SpO_2 89%.
- Ventilator settings – AC/VC; Vt 4 mL/kg PBW, FiO_2 70%, PEEP 12 cm H_2O.

Clinical scenario #3 – con't

- You continue ARDSnet IMV low(er) PEEP/high(er) FiO2 and LTVV strategy and start appropriate antiviral/antibacterial therapy, prone positioning, and alert the on-call ECMO physician about a potential VV-ECMO candidate.
- Your resident team asks – should we start steroids?

Steroids in the critically ill adult

- Probably the most controversial topic in critical care.
- Inconsistent, poorly reproducible results in various trials.
- Providers with differing opinions, result is staff never really knows what to expect/how to protocolize.

  →Enter the 2024 Focused Update: Guidelines on the Use of Corticosteroids in Sepsis/ARDS/CAP and the newest iteration of Surviving Sepsis Guidelines.

SCCM – 2024 Focused Update

- 22-member expert panel (intensivist, endocrinologists, pulmonologists, nursing) reviewing best available evidence to produce answers to five clinical questions:
  1.) Should steroids be administered to hospitalized patients with sepsis?
  2.) What is the ideal dose/duration for patients with sepsis?
  3.) Should steroids be used in patients with ARDS?
  4.) Should methylprednisolone be used preferentially in ARDS?
  5.) Should steroids be administered to hospitalized patients with CAP?

Opinion of the panel…

Voting Results

Recommendation	Response Rate (%)	Yes (%)	No (%)	Abstain (%)
1. We **suggest** administering corticosteroids to patients with septic shock.	100%	90%	0%	10%
2. We **recommend against** administration of high dose/short duration corticosteroids (>400mg/day hydrocortisone equivalent for less than 3 days) for septic shock.	100%	95%	0%	5%
3. We **suggest** administering corticosteroids to hospitalized patients with acute respiratory distress syndrome.	100%	100%	0%	0%
4. We **recommend** corticosteroids for patients hospitalized with severe bacterial community acquired pneumonia.	100%	100%	0%	0%
5. We make **no recommendation** for corticosteroids for patients hospitalized with less severe bacterial community acquired pneumonia.	100%	100%	0%	0%

Voting panel members n=20

SCCM 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, ARDS, and CAP

- *Should corticosteroids be administered to hospitalized patients with sepsis?*
  - Existing Surviving Sepsis Guideline recommends when patient fails to meet MAP goals on moderate-dose vasopressor therapy (defined in SS document as 0.25 mcg/kg/min of norepinephrine).
- 46 RCTs have investigated the benefit of CS versus placebo.
  - Majority (30) → septic shock.
  - 7 → Sepsis.
  - 5→ CAP and sepsis.
  - 4 → ARDS and sepsis.
- Variable CS of choice, dose, duration.

SCCM 2024 – steroids in sepsis/septic shock

- Panel opinion – CS use…
  - Results in higher rate of shock reversal and reduced organ dysfunction) at 7 days.
  - *May* reduce hospital long-term mortality and *probably* reduces ICU short-term mortality in patients with sepsis and septic shock.
  - *May* reduce ICU and hospital length of say.
  - *May* increase neuromuscular weakness.
  - *Probably* increases frequency of hyperglycemia and hypernatremia.
  - *May* reduce neuropsychiatric effects.
  - Uncertain effect on GI bleeding, superinfection, CVA, and MI.

SCCM 2024 – steroids in sepsis/septic shock con’t

- *What is the ideal dose/duration of corticosteroids in sepsis?*
  - No head-to-head trials; older studies of shorter-duration/higher-dose regimens are not more effective but are associated with greater risk of adverse effects.
  - Recommendation for agents/doses/durations similar to what has been used in modern studies evaluating use of steroids in septic shock (hydrocortisone 200 mg/day in divided doses).

SCCM 2024 – Steroids in ARDS

- *Should corticosteroids be administered to patients with ARDS?*
  - ARDSnet trials showed lack of benefit with early and risk of harm with late (beyond 14 days) steroids in patients with ARDS.
  - SCCM panel identified 18 RCTs investigating CS to SOC in ARDS.
    - **NOTE:** 6 of these were conducted in COVID ARDS.

SCCM 2024 – Steroids in ARDS

- Opinion – CS in ARDS…
  - *Reduces* IMV days and hospital LOS (not ICU LOS).
  - *Probably* reduces 28-day mortality in critically ill patients with ARDS.
  - Subgroup analyses of CS type, dose yielded no significant differences.
  - Treatment duration was the only meaningful subgroup, > 7 days CS outperformed < 7 days.

SCCM 2024 – Steroids in CAP

- *Should corticosteroids be administered to patients with severe **bacterial** CAP?*
- Panel reviewed 18 RCTs comparing CS+SOC to SOC alone
  - 10 included patients with “severe” disease (PSI class 4-5, CURB-65 >/= 22).
  - 8 included patients with “less severe” disease.
- CS in **severe <u>bacterial</u>** CAP…
  - *Probably* reduce hospital mortality.
  - *Probably* reduce the need for IMV.
  - *May* reduce duration of ICU and hospital stay.
  - *Probably* increase risk of hyperglycemia, secondary infections.
  - *Uncertain* effects on GI bleeding, NM weakness, NS effects, etc.

Definitions of *severe* (bacterial) CAP

TABLE 5. - Severe Community-Acquired Pneumonia Definitions

Source	Definition
American Thoracic Society/Infectious Diseases Society of America Criteria 2007[a] ([92])	Either one major criterion or three or more minor criteria: Major criteria • Septic shock with need for vasopressors • Respiratory failure requiring mechanical ventilation Minor criteria • Respiratory rate ≥ 30 breaths/min[b] • Pao_2/Fio_2 ratio ≤ 250[b] • Multilobar infiltrates • Confusion/disorientation • Uremia (blood urea nitrogen level ≥ 20 mg/dL) • Leukopenia (WBC count < 4000 cells/μL)[c] • Thrombocytopenia (platelet count < 100,000/μL) • Hypothermia (core temperature < 36°C) • Hypotension requiring aggressive fluid resuscitation
Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE COD) ([67])	One of four criterion: • Initiation of mechanical ventilation (invasive or noninvasive) with a positive end-expiratory pressure level of at least 5 cm of water • Administration of oxygen through a high-flow nasal cannula with a Pao_2/Fio_2 ratio of < 300, with a Fio_2 of ≥ 50% • Nonbreathing mask with estimated Pao_2/Fio_2 of < 300, according to prespecified charts • Pulmonary Severity Index score of > 130 (group V) Inclusion in study required ICU admission
Risk Stratification Scores	• Pneumonia severity index class IV or V ([93]) • Confusion, urea nitrogen, respiratory rate, blood pressure-65 score of ≥ 3 ([94]) • Confusion, oxygenation, respiratory and blood pressure score of ≥ 2 ([95]) • Systolic blood pressure, multilobar chest radiography, albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH score ≥ 3 ([96])

[a]Studies used previous iterations of ATS criteria modified by Ewig et al ([97]).
[b]A need for noninvasive ventilation can substitute for a respiratory rate ≥ 30 beats/min or a Pao_2/Fio_2 ratio ≤ 250.
[c]As result of infection alone.

TABLE 4. - Corticosteroid Dosing Regimens

Disease State	Common Corticosteroid Regimens
Septic shock	Hydrocortisone 200 mg IV per day (continuous infusion or divided every 6 hr) with or without fludrocortisone 50 µg enteral daily for 7 d or until ICU discharge[a]
ARDS	Early ARDS (within 24 hr) Dexamethasone 20 mg IV daily for 5 d, then 10 mg IV daily for 5 d until extubation ([64]) Early ARDS (within 72 hr) ([65]) Methylprednisolone 1 mg/kg IV bolus, then • Days 1–14: 1 mg/kg/d continuous infusion • Days 15–21: 0.5 mg/kg/d • Days 22–25: 0.25 mg/kg/d • Days 26–28: 0.125 mg/kg/d • If extubated between days 1 and 15 then advance to day 15 of regimen Unresolving ARDS (7–21 d) ([26]) Methylprednisolone 2 mg/kg IV bolus, then • Days 1–14: 2 mg/kg/d divided every 6 hr • Days 15–21: 1 mg/kg/d • Days 22–28: 0.5 mg/kg/d • Days 29–30: 0.25 mg/kg/d • Days 31–32: 0.125 mg/kg/d • If extubated before day 14, then advance to day 15 of regimen drug therapy
Severe community-acquired bacterial pneumonia	Hydrocortisone 200 mg IV once, then 10 mg/hr IV infusion for 7 d ([14], [66]) Hydrocortisone 200 mg IV daily (for 4 or 8 d based on clinical improvement), then taper (for a total duration of 8 or 14 d duration) ([67]) • Hydrocortisone discontinued on ICU discharge Methylprednisolone 0.5 mg/kg IV every 12 hr for 7 d (within 36 hr of hospital admission, C-reactive protein >150 mg/L) ([46]) Methylprednisolone 40 mg IV bolus, then • Days 1–7: 40 mg/d • Days 8–14: 20 mg/d • Days 15–17: 12 mg/d • Days 18–20: 4 mg/d • Administered via continuous infusion in ICU, then changed two divided bid, via IV or enteral, after ICU discharge ([68])

Clinical scenario #4

HPI: 52 year old female presents with severe hypoxemia necessitating 15L NRB; CXR demonstrates dense consolidative opacities bilaterally.

- Patient is intubated and admitted to ICU.
- Cultures obtained, broad-spectrum antibiotics initiated.
- Resuscitated with isotonic crystalloid, vasopressors initiated to maintain MAP.
- FSBG consistently 250-300 mg/dL.

-What action is required?

1.) Initiate titratable insulin infusion to maintain FSBG 80-120 mg/dL.

2.) Administer rapid-acting SC insulin to achieve FSBG 140-180 mg/dL.

3.) Administer rapid-acting SC insulin to achieve FSBG 140-200 mg/dL.

2024 SCCM Guidelines for Glycemic Control in Critically Ill Adults

In "adult critically ill patients," should we recommend initiating IV insulin therapy at a lower glucose threshold 6.1–10 mmol/L (110–180 mg/dL) or higher glucose threshold > 10 mmol/L (> 180 mg/dL)?

- Panel opinion:
  - Treat persistent hyperglycemia >/= 180 mg/dL.
  - Recommendation against lower glycemic targets (80-139 mg/dL).
  - Preference for conventional targets (140-200 mg/dL).
- CVICU and NCC patients should be managed similarly to unselected patients (e.g. MICU, SICU).
  - (2006) Study demonstrating improved mortality with lower targets in post-cardiac surgery patients couldn't be reproduced in five subsequent RCTs.
  - Lower glycemic targets consistently associated with risk of severe hypoglycemia.

2024 SCCM Guidelines for Glycemic Control in Critically Ill Adults

"In the acute management of adult critically ill patients for whom insulin therapy is being initiated," should we recommend initiating continuous IV insulin infusion "or" intermittent subcutaneous insulin?

- Panel opinion:
  - "We suggest using continuous IV insulin infusion rather than intermittent subcutaneous dosing in the acute management of hyperglycemia in critically ill adult patients.
- Six studies (two RCT, four observational) evaluation continuous IV versus intermittent SC insulin dosing.
  - IV infusion more likely to achieve target glycemic control.
  - No meaningful difference in other outcomes (mortality, ICU LOS, infections).
  - Greater likelihood of severe hypoglycemia with IV insulin.
  - Panel preference for IV insulin seems to derive from concerns about absorption and burden of monitoring/nocturnal awakenings for SC administration.

2024 SCCM Guidelines for Glycemic Control in Critically Ill Adults

"In adult critically ill patients on insulin infusion therapy," should we recommend monitoring of glucose at frequent intervals (≤ 1 hr, continuous or near-continuous) "or" longer intervals (> 1 hr), during the period of glycemic instability?

- "We suggest frequent (</= 1 hour, continuous, or near-continuous) glucose monitoring compared with intervals greater than hourly for patients receiving IV insulin during periods of glycemic instability.

Clinical scenario #5

HPI: 23 year old male presents with depressed LOC, HAGMA, blood glucose > 400 mg/dL, and ketonemia.

- Serum potassium 3.1 mEq/L, PO4 < 0.9, iCal 0.9.
- ABG demonstrates pH 6.9, PaCO2 19 mmHG.

- You rapidly correct electrolytes, repeat potassium 3.8 mEq/L, continuous fixed-rate insulin infusion started in conjunction with potassium-containing fluids.

Clinical scenario #5 – con't

- Repeat laboratory studies demonstrate:
  - Na+ 140 mEq/L; Cl- 115 mEq/L; K+ 3.7 mEq/L
  - AG 18; HCO3- 14 mmol/L
  - Glucose 200 mg/dL
- Your choice of fluid?

  1.) D5 in 0.9% NaCl + KCl 40 mEq/L.

  2.) D5 in 0.45% NaCl + KCl 40 mEq/L.

  3.) D5 in Plasmalyte + KCl 40 mEq/L.

Diabetic ketoacidosis - definition

- ADA 2009 – Hyperglycemic Crises in Adult Patients with Diabetes
  – “…serious acute metabolic complication of diabetes…characterized by the triad of uncontrolled hyperglycemia, metabolic acidosis, and increased total body ketone concentration”

  - 10% “euglycemic” DKA defined by serum glucose concentration of </= 250 mg/dL

ADA/EASD/JBDS/AACE/DTS 2024 criteria

DKA	**A. DKA Diagnostic Criteria**	
	Diabetes/hyperglycemia	Glucose ≥200 mg/dL (11.1 mmol/L) OR prior history of diabetes
	Ketosis	β-Hydroxybutyrate concentration ≥3.0 mmol/L OR urine ketone strip 2+ or greater
	Metabolic **A**cidosis	pH <7.3 and/or bicarbonate concentration <18 mmol/L
HHS	**B. HHS Diagnostic Criteria**	
	Hyperglycemia	Plasma glucose ≥600 mg/dL (33.3 mmol/L)
	Hyperosmolarity	Calculated effective serum osmolality >300 mOsm/kg (calculated as [2xNa^+ (mmol/L) + glucose (mmol/L)]), OR total serum osmolality >320 mOsm/kg [(2xNa^+ (mmol/L) + glucose (mmol/L) + urea (mmol/L)]
	Ab**S**ence of significant ketonemia	β-Hydroxybutyrate concentration <3.0 mmol/L OR urine ketone strip less than 2+
	Absence of acidosis	pH ≥7.3 and bicarbonate concentration ≥15 mmol/L

ADA 2009 consensus statement

	DKA		
	Mild (plasma glucose >250 mg/dl)	Moderate (plasma glucose >250 mg/dl)	Severe (plasma glucose >250 mg/dl)
Arterial pH	7.25–7.30	7.00 to <7.24	<7.00
Serum bicarbonate (mEq/l)	15–18	10 to <15	<10
Urine ketone*	Positive	Positive	Positive
Serum ketone*	Positive	Positive	Positive
Effective serum osmolality†	Variable	Variable	Variable
Anion gap‡	>10	>12	>12
Mental status	Alert	Alert/drowsy	Stupor/coma

ADA et al 2024 classification of severity

Table 2—DKA classification and suggested level of care by severity: mild, moderate, or severe

	Mild DKA	Moderate DKA	Severe DKA
"D": history of diabetes or elevated glucose level	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)	Glucose ≥200 mg/dL (11.1 mmol/L)
"K": ketonemia	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate 3.0–6.0 mmol/L	β-Hydroxybutyrate >6.0 mmol/L
"A": acidosis	• pH >7.25 to <7.30 or bicarbonate 15–18 mmol/L	• pH 7.0–7.25 • Bicarbonate 10 to <15 mmol/L	• pH <7.0 • Bicarbonate <10 mmol/L
Mental status	Alert	Alert/drowsy	Stupor/coma
Suggested level of care	Regular or observation nursing unit	Step-down unit or intermediate care unit	Intensive care unit

Not all variables need to be fulfilled to be defined as either mild, moderate, or severe, and the admission site and level of care are ultimately a clinical decision.

DKA – core tenets of management

1.) Volume expansion to restore tissue perfusion

2.) Correction of electrolyte abnormalities

3.) Insulin administration to correct metabolic defect

Tenet #1 – fluid resuscitation

- Directed toward expansion of intravascular, interstitial, and intracellular compartments
- ADA 2009 consensus - 15-20 mL/kg isotonic saline during first hour
  - Patient hyperglycemic and insulin deficient → no supplemental dextrose
- Beyond first hour, ADA recommendation varies with corrected serum sodium
  - Hyper/eunatremia – 0.45% NaCl @ 250-500 mL/h
  - Hyponatremia – 0.9% NaCl @ 250-500 mL/h

ADA et al 2024 – fluid resuscitation

- “The fluid choice for initial resuscitation should be determined by local availability, cost, and resources.”
  - Current guideline ONLY mentions isotonic crystalloid.
  - 500-1000 mL/h x 2-4 hours, then correction of remaining deficit over 24-48 hours.
- Cites potential impact of NS versus LR or PL in terms of NAGMA, ICU LOS.

DKA – fluid resuscitation (con't)

- Horng-Ruey C et al (2012) – Plasma-Lyte 148 vs 0.9% NaCl for DKA
  - Retrospective analysis of 23 adults with DKA
  - 0.9% NaCl (n=9); Plasma-Lyte 148 (n=14)
- Serum bicarbonate higher in PL group
  - Increase of 8.4 vs 1.7 mEq/L at 4-6 hr; 12.8 vs 6.2 at 6-12 hr ($p < 0.05$)
- Chloride higher in NS group
- UOP higher in PL group at 4-6 hours
- No difference in glycemic control or ICU length of stay

0.9% NaCl vs balanced crystalloid (con't)

- Mahler S et al (2011) – prospective, double-blind RCT (n = 52)
  - Plasma-Lyte A vs 0.9% NaCl
  - Post-resuscitation chloride 105 vs 111 ($p < 0.001$) at 4 hours
  - Bicarbonate 20 vs 17 ($p = 0.02$)
- Van Zyl D et al (2012) – prospective, double blind RCT (n = 57)
  - Lactated Ringer's vs 0.9% NaCl
  - Median time to reach pH 7.32 540 vs 638 minutes ($p = 0.251$)
  - Time to euglycemia 410 vs 300 min ($p = 0.044$)
  - No difference in time to resolution of DKA
- Joint British Diabetes Societies (2013) – recommend 0.9% NaCl

Bicarbonate in DKA – yes or no?

- ADA (2009) – yes, if pH < 6.9
  - 100 mmol in 400 mL water + KCl 20 mEq for two hours; repeat until pH > 7
- ADA (2024) – yes, if pH < 7.0
- British guidelines (2013) – no, not ever
  - Possibly worse outcomes in children and young adults?
  - Glaser N et al (2001) – retrospective study of 61 children with DKA who developed cerebral edema
    - Relative risk of 4.2 (p = 0.008) among those who received IV bicarbonate
- Multiple negative studies; recommendation from ADA is made in recognition of untoward CV effects of severe acidemia
  - Most studies compared *resuscitation* with bicarbonate versus 0.9% NaCl

Fluid administration - dextrose

- ADA 2009
  - “When serum glucose reaches 200 mg/dL, change to 5% dextrose plus 0.45% NaCl…”
- ADA 2024
  - “…once the plasma glucose concentration is < 250 mg/dL, replacement fluids should be modified to contain 5–10% dextrose in addition to the 0.9% sodium chloride…”
- British 2013
  - “Introduction of 10% glucose is recommended when blood glucose falls below 14 mmol/L. It is important to continue 0.9% sodium chloride solution to correct circulatory volume.”

Tenet #2 – electrolyte abnormalities

- Potassium deficit typically 3-5 mEq/kg (210-350 mEq)
  - Also true for those presenting with hyperkalemia
  - Insulin deficiency, acidemia → decreased activity of Na-K ATPase
- Potassium replacement begins when serum level is at upper range of normal (5 – 5.2 mEq/L)
  - ADA 2009 consensus statement
    - Goal → maintain K in range of 4-5 mEq/L
    - If serum K < 5.2, add 20-30 mEq/L of resuscitative fluid
    - If serum K < 3.3, give 20-30 mEq per hour until >3.3 mEq/L
  - ADA 2024 → essentially no change

Hypokalemia in DKA

- ADA 2024 - if serum K < 3.5, STOP INSULIN.
  - Change from previous recommendation of 3.3 mEq/L.
  - Severe hypokalemia (< 2.5 mEq/L) plus insulin therapy → threefold greater mortality.
- ADA 2024 – monitoring of potassium
  - Recheck 2 hours after starting insulin, then q4h thereafter.

Phosphate and DKA

- Hypophosphatemia detected in 80% (probably more) cases of DKA
  - Average deficit 1 mmol/kg
  - Serum concentration may be normal/elevated on presentation
- Historically, concern related to 2,3 DPG depletion
- Effects are broad and impact nearly every system; read – ATP depletion
  - CNS – encephalopathy, paresthesia, weakness, seizure
  - CV – heart failure, arrhythmia
  - Pulm – hypoventilation (diaphragmatic weakness)
  - Hematologic – hemolysis, impaired granulocyte function
  - MSK – rhabdomyolysis

Phosphate in DKA - replacement

- ADA 2009 consensus
  - "…careful phosphate replacement may sometimes be indicated in patients with cardiac dysfunction, anemia, respiratory depression, and in those with phosphate concentration < 1 mg/dL…
- ADA 2024 consensus
  -"…unless there is evidence of muscle weakness, such as respiratory or cardiac compromise with the phosphate < 1.0 mmol/L, routine administration of phosphate is not indicated."
- British 2013 consensus
  - "…we do not recommend the routine measurement or replacement of phosphate...in the presence of skeletal and respiratory muscle weakness, phosphate measurement and replacement should be considered."

Phosphate and DKA - evidence

- Fisher et al (1983) – prospective, randomized study in 30 pt with DKA
  - 15 pt randomized to receive 8.5 mmol/hour for 48 hours vs 15 pt randomized to NO replacement
  - Higher incidence of hypocalcemia with phosphate replacement
  - No difference in time to resolution of DKA, incidence of respiratory failure, or resolution of coma
- Other studies are similarly (very) old and used continuous phosphate infusions…

Tenet #3 - Insulin and DKA

- ADA 2009 - decrease FSBG by 50-75 mg/dL (~10%) within one hour
  - If goal not met, give 0.14 unit/kg IV x 1, continue prior infusion rate
- British 2013
  - Decrease serum glucose by 50-60% within first four hours
  - Lower risk of osmotic shift-related adverse effects compared to HHS
- Maintain between 150-200 until resolution of DKA

Insulin and DKA – rate

- Both societies recommend regular insulin protocol
  - ADA 2009 – bolus (0.1 unit/kg IV x1) followed by 0.1 unit/kg/hr IV -OR- no bolus with 0.14 units/kg/hr IV
  - ADA 2024 - initial 0.1 unit/kg IV bolus followed by fixed-rate infusion at 0.1 unit/kg/hr
  - British 2013 – no bolus, 0.1 unit/kg/hr fixed-rate infusion
- Kitabchi AE et al (2008) – prospective RCT of 37 patients with DKA
  - Group 1 (n=12): 0.07 unit/kg IV load, then 0.07 unit/kg/hr IV
  - Group 2 (n=12): no load, 0.07 units/kg/hr IV
  - Group 3 (n=13): no load, 0.14 units/kg/hr IV
    - No difference in time to resolution of DKA in groups 1 and 3; group 2 required additional doses

Insulin and DKA – rate (con't)

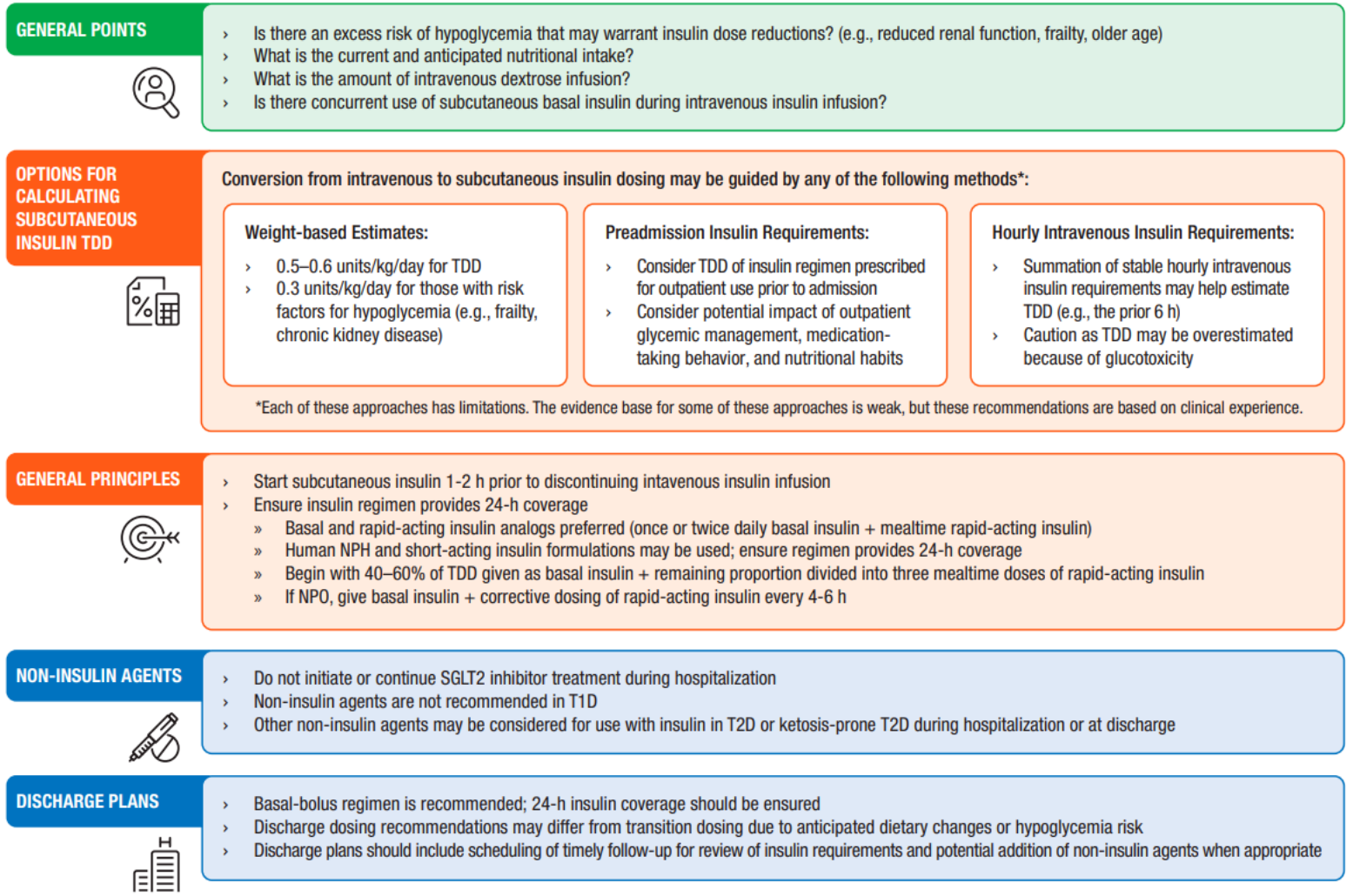
- ADA 2009
  - When serum glucose reaches 200 mg/dL, reduce to 0.02 – 0.05 units/kg/hr IV
    - Subsequent insulin titration to maintain FSBG 150-200 mg/dL

    - OR -
  - Give rapid-acting insulin (Novolog, Humalog, Apidra) 0.1 units/kg IV q2h
    - Caveat: not recommended for "severe DKA" (expert opinion)
- ADA 2024
  - When glucose reaches 250 mg/dL, reduce to 0.05 units/kg/hr IV

Basal insulin during initial tx for DKA?

- British 2013 consensus
  - Recognized as a “controversial topic”
  - Suggestion to use during initial phase of treatment is based on clinical experience
  - Rationale: prevents rebound hyperglycemia when infusion is stopped
- Hsia E et al (2012)
  - Prospective, randomized study of 61 pt with DM receiving IV insulin (not exclusively DKA…)
    - Excluded “newly diagnosed hyperglycemia” and “critically ill” patients
  - Goal: determine incidence of hyperglycemia after discontinuation of IV insulin
    - Intervention → received Lantus 0.25 units/kg IV within 12 hours of initiation of IV insulin
    - Control → IV insulin alone
  - Greater incidence of “rebound hyperglycemia” in control group (93.5 vs 33.3)
- ADA 2024
  - Coadministration of basal insulin (0.15-0.3 U/kg) with fixed-rate IV “is advocated by many but avoided by others”.
  - Reduces time to resolution of DKA, less rebound hyperglycemia.

Transitioning – ADA 2024



Discussion

- Targeted temperature management.
- Steroids in CAP/ARDS/septic shock
- Glycemic management in critically ill adults
- DKA updates

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