Topics

1. Antithrombotic therapy for VTE from CHEST 2021
2. Updated heart failure guidelines
3. Use of contrast media in renal disease
4. Adoption of dual antiplatelet therapy for secondary prevention of ischemic stroke in clinical practice
5. Saline versus balanced crystalloid debate
6. PICC versus mid line catheters
55 year old female with abdominal pain

- Endoscopy and biopsy reveal gastric adenocarcinoma. Day 2 she has a proximal DVT in the left leg. What is the appropriate choice?

A.) Inferior vena cava filter
B.) Low molecular weight heparin dosed 1 mg/kg twice daily
C.) Apixaban 10 mg twice daily for 7 days, then 5 mg twice daily
D.) Vitamin K antagonist (warfarin) bridged with low molecular weight heparin
E.) Rivaroxaban 15 mg twice daily for 21 days, then 20 mg once daily
Cancer-associated VTE

- Oral Xa inhibitor

Apixaban
Edoxaban
Rivaroxaban

Oral Xa inhibitor > LMWH for cancer related VTE

Intraluminal GI malignancies

- Apixaban or low molecular weight heparin (LMWH)

  • ↓ Bleeding risk than other Xa inhibitors
Coagulation pathways
Warfarin

![Graph showing the decline of coagulant activity, percent, log scale over days after warfarin ingestion. The graph illustrates the decay of factors VII, IX, X, Prothrombin, and Protein C over time.](image)

2022 Uptodate. Graphic 50490; version 2.0.
DOACs

Figure courtesy of George A. Fritsma; The Fritsma Factor, Your Interactive Hemostasis Resource
TF, tissue factor; pre-K, pre-kallikrein; HMWK, high molecular weight kininogen; DTI, direct thrombin inhibitor, Thr, thrombin
2021 Updated CHEST Guidelines

- Cancer associated VTE
- Antiphospholipid syndrome
- Extended-phase therapy (beyond 3 months)
- Catheter-assisted mechanical thrombectomy
- Incidentally discovered asymptomatic PE
- Treatment-phase anticoagulants
- Initial anticoagulation setting
- Isolated sub segmental PE
68-year-old male is admitted with shortness of breath and lower extremity swelling.

**PMH:** HTN, non-ischemic cardiomyopathy EF 30%

**Meds:** Carvedilol, losartan, spironolactone, furosemide

**Vitals:** 145/90 mmHg, 70 BMP

**PE:** ↑JVP, S3 with RR, + crackles

**CXR:** Pulm edema, intact AICD

**Labs:** K 3.5, Crea1.4 and FBG 80

**EKG:** NSR with QRS width of 120 ms, no acute ST changes
Which of the following should be considered...

• To reduce further hospitalizations and cardiovascular mortality and improve quality of life after discharge?

• A.) Low dose digoxin
• B.) Low sodium diet
• C.) Dapagliflozin 10 mg daily
• D.) Exchange of defibrillator to combo biventricular pacemaker/defibrillator
• E.) Addition of metolazone to furosemide
2022 AHA/ACC/HFSA Guidelines

- Symptomatic chronic HFrEF
  - Irrespective of diabetes

- SGLT2 (sodium-glucose co-transporter 2) inhibitors
  - ↓ heart failure
  - ↓ cardiovascular mortality
  - Intermediate economic value
Schematic diagram showing conventional mechanisms of action of SGLT2 inhibitors.

- Reduced ATP consumption in PCT and relative hypoxia in renal cortex
- Reversion of myofibroblasts to Erythropoietin producing fibroblasts
- Increased glucagon vs insulin ratio
- Reduced plasma volume and improved endothelial function
- Reduction in blood pressure and afterload
- Reduction in ventricular preload
- Increased urinary Na+ and Glucose excretion
- Lipolysis
- Increased Hematocrit
- Weight loss
- Improved ventricular loading conditions

© 2020 S Joshi

Shruti S Joshi et al. Heart 2021;107:1032-1038
Copyright © BMJ Publishing Group Ltd & British Cardiovascular Society. All rights reserved.
DAPA-HF and EMPEROR-Reduced Trials

- SGLT2i > placebo
  ↓ composite of cardiovascular death or HF hospitalizations by 25%.

- Benefit in reduction of HF hospitalizations alone
  >30% in both trials.

- Improved renal outcomes

- Irrespective of diabetes

EMPEROR-Preserved Trial

SGLT2 inhibitors (empagliflozin) in preserved EF (greater than 40%)

↓ in risk of CV death or HF hospitalization.

Overall health status and quality of life scores improved **early** after initiation
Sustained ≥ 1 year.

Safety concerns

- Genitourinary infections
- Euglycemic ketoacidosis
- Soft tissue infections
- Increase in risk for amputations
- Volume depletion in combination with other diuretics.
SGLT2 inhibitors

- Improve CV outcomes
- ↓ Hospitalizations
- ↑ Quality of life across a broad range of heart failure types
- Effects occur regardless of background of other GDMT
- Irrespective of diabetes
49-year-old male with obesity, OSA, HTN and CKD stage 3a

Admitted with chest pain

Clear CXR, ↑ D-dimer 600 ng/ml and mild troponin elevation.

EKG with sinus tachycardia but no ST changes

Empirically treated with IV infusion of unfractionated heparin and admitted

ED wanted to R/O PTE with CT angiogram, but did not because creatinine 2.0 mg/dL
Which of the following is true?

A.) Iodinated contrast, especially in a CT angiogram, can cause worsening kidney function in a patient with underlying CKD and should be avoided if possible.

B.) Risk of AKI or worsening renal dz from iodinated contrast has been overestimated in the past and is generally safe in this population.

C.) Hemodialysis immediately after a contrasted study has been shown to reduce the risk of contrast induced nephropathy.

D.) Iodinated contrast studies are safe, but images (such as MRI) using gadolinium based agents should be avoided in patients with CKD because of the risk of nephrogenic systemic fibrosis.
Current Intravenous Contrast Agents

The American College of Radiology and the National Kidney Foundation

Consensus statement in 2020 regarding use of iodinated contrast media in patients with kidney disease

↓ in osmolality
Generally can be administered safely
Minimal risk of acute kidney injury or worsening long term renal function

Proposed mechanism of CIN

- Vasoconstriction
  - Ca++ influx
  - Endothelin release
  - Selective vasoconstriction in corticomedullary junction
  - Impaired vasodilation
  - Duration up to 4 hours

- Vasodilation
  - Medullary hypoxia
  - $\text{PaO}_2$ 15–20 mm Hg
  - Vasoconstriction
  - Impaired vasodilation
  - ↓NO production

- Direct tubular toxicity
  - Oxidative stress
  - OH$^-$, O$_2^-$ free radicals
Contrast and kidneys

• Iodinated contrast is ↓ in osmolality than past agents

• New evidence → risk for contrast associated AKI negligible if eGFR of > 30 ml/minute
  • Safe, especially if the contrasted study will change management

Contrast and Kidneys

• eGFR < 30 ml/minute
  – Volume expand with isotonic saline and avoid nephrotoxic agents

• Intra-arterial (cardiac catheterization) not included in the statement
  • CT angiogram utilized for PTE evaluation is an intravenous, not intra-arterial administration.

Review of the literature

• Iodinated contrast historically thought to be nephrotoxic
  • However→ many observational studies found no evidence of an association

• Observational studies→ risk of confounding and selection bias
  • Those at highest risk of kidney injury were given non contrasted studies

Review of the literature

- Recent cohort study design enabled more robust evaluation of the association between radiocontrast and acute kidney injury
  - Regression discontinuity design

Literature Review

- Canadian study evaluating 156,028 individuals who received a D-dimer test in the emergency department between 2013-2018
  - Exposure was contrast in the form of CTPA
  - Primary outcome
    - Estimated eGFR up to 6 months following the emergency department visit
    - No evidence that contrast changed eGFR up to 6 months later
    - No association with need for kidney replacement therapy

Literature Review

- Subgroup analyses underpowered but suggested harm in diabetes

- No harm found in those with other reported risk factors for “CIN”
Gadolinium

- Risk for nephrogenic systemic fibrosis is rare and occurs exclusively in type 1 gadolinium media

- This agent is no longer available in the US
75 year old male with hypertension and diabetes

- Presents to the emergency department 8 hours of dizziness, progressive dysphagia, blurry vision, and loss of sensation in the face.

- Neuroimaging reveals stenosis of the distal portion of the intracranial vertebral artery near the vertebral-basilar artery junction.

- At bedside, the National Institutes of Health Stroke Scale NIHSS= 6
<table>
<thead>
<tr>
<th>NIH Stroke Scale Score</th>
<th>Stroke Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No stroke symptoms</td>
</tr>
<tr>
<td>1-4</td>
<td>Minor stroke</td>
</tr>
<tr>
<td>5-15</td>
<td>Moderate stroke</td>
</tr>
<tr>
<td>16-20</td>
<td>Moderate to severe stroke</td>
</tr>
<tr>
<td>21-42</td>
<td>Severe stroke</td>
</tr>
</tbody>
</table>
| 1a—Level of consciousness                  | 0 = Alert; keenly responsive  
|                                          | 1 = Not alert, but arousable by minor stimulation  
|                                          | 2 = Not alert; requires repeated stimulation  
|                                          | 3 = Unresponsive or responds only with reflex  
| 1b—Level of consciousness questions:     | 0 = Answers two questions correctly  
| What is your age?                        | 1 = Answers one question correctly  
| What is the month?                       | 2 = Answers neither questions correctly  
| 1c—Level of consciousness commands:      | 0 = Performs both tasks correctly  
| Open and close your eyes                 | 1 = Performs one task correctly  
| Grip and release your hand               | 2 = Performs neither task correctly  
| 2—Best gaze                              | 0 = Normal  
|                                          | 1 = Partial gaze palsy  
|                                          | 2 = Forced deviation  
| 3—Visual                                 | 0 = No visual lost  
|                                          | 1 = Partial hemianopia  
|                                          | 2 = Complete hemianopia  
|                                          | 3 = Bilateral hemianopia  
| 4—Facial palsy                           | 0 = Normal symmetric movements  
|                                          | 1 = Minor paralysis  
|                                          | 2 = Partial paralysis  
|                                          | 3 = Complete paralysis of one or both sides  
| 5—Motor arm                              | 0 = No drift  
| Left arm                                 | 1 = Drift  
| Right arm                                | 2 = Some effort against gravity  
|                                          | 3 = No effort against gravity  
|                                          | 4 = No movement  
| 6—Motor leg                              | 0 = No drift  
| Left leg                                 | 1 = Drift  
| Right leg                                | 2 = Some effort against gravity  
|                                          | 3 = No effort against gravity  
|                                          | 4 = No movement  
| 7—Limb ataxia                            | 0 = Absent  
|                                          | 1 = Present in one limb  
|                                          | 2 = Present in two limbs  
| 8—Sensory                                | 0 = Normal; no sensory loss  
|                                          | 1 = Mild-to-moderate sensory loss  
|                                          | 2 = Severe-to-total sensory loss  
| 9—Best language                          | 0 = No aphasia; normal  
|                                          | 1 = Mild-to-moderate aphasia  
|                                          | 2 = Severe aphasia  
|                                          | 3 = Mute; global aphasia  
| 10—Dysarthria                            | 0 = Normal  
|                                          | 1 = Mild-to-moderate dysarthria  
|                                          | 2 = Severe dysarthria  
| 11—Extinction and inattention            | 0 = No abnormality  
|                                          | 1 = Visual, tactile, auditory, spatial, or personal inattention  
|                                          | 2 = Profound hemi-inattention or extinction  

Score = 0–42

Figure 1. The National Institutes of Health Stroke Scale (NIHSS).  
Note: NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurological impairments.
Which of the following is the best regimen to reduce the risk of recurrent ischemic stroke?

- A.) Dual antiplatelet therapy with aspirin and clopidogrel for 21 days
- B.) Monotherapy with aspirin or clopidogrel indefinitely
- C.) Dual antiplatelet therapy with aspirin or clopidogrel for 90 days
- D.) Apixaban 2.5 mg twice daily
Dual Antiplatelet therapy (DAPT)

• Secondary Prevention in US Patients with Acute Ischemic Stroke

• Historically→ DAPT (aspirin plus clopidogrel) not recommended because of excessive bleeding risk
But Then….

• CHANCE (Clopidogrel in High Risk Patients with Acute Non-Disabling Cerebrovascular Events) trail and the POINT (Platelet Oriented Inhibition in New TIA and Minor Ischemic Stroke)

  • Short term DAPT (21-90 days) in patient with a NIHSS score ≤ 3
    • DAPT ↓ the risk of recurrent ischemic stroke.

• AHA (American Heart Association) and ASA (American Stroke Association) updated their recommendations to benefit>>risk (class I, level A) in favor of short term DAPT for minor stroke or TIA
Retrospective review

- 1,281,034 patients hospitalized for acute ischemic stroke and prescribed antiplatelet therapy at discharge
  - 2,228 hospitals in the Get With The Guidelines-Stroke registry

- Antiplatelet agents prescribed at discharge were evaluated
  - 5 periods based on the dates of the CHANCE and POINT trial publications and the 2014, 2018, and 2019 AHA/ASA guideline updates.
Translation to Clinical Practice

- Use of DAPT gradually increased over the years
  - 19.4% before CHANCE trial → 44.9 % after 2019 AHA/ASA guidelines

- DPAT is indicated only for minor strokes and TIAs with NIHSS score ≤ 3
  BUT Increases in use were observed for all strokes
  - Minor strokes
    - (19%→47.0%)
  - Non minor strokes with an NIHSS score ≥ 3
    - (19%→42.6%)

Translation to clinical practice

- After the 2019 AHA/ASA guideline updates, only 47% of patients with minor strokes received DAPT
  
  * Underuse of DAPT in minor strokes

- ≥ 42% of patients with non minor strokes (median NIHSS score = 6) were prescribed DAPT at discharge
  
  * Overuse of DAPT in non minor strokes

In Conclusion

• Increased adoption of DAPT for secondary prevention in ischemic stroke observed after publication of 2 pivotal trials and serial AHA/ASA guideline updates

• Suggests an opportunity to improve adherence to evidence-based antiplatelet therapy for secondary prevention in patients with acute ischemic stroke
Which is true regarding IV fluids?

• A.) 0.9% saline is preferred because of the risk of hyponatremia in critically ill patients

• B.) Balanced solutions, such as Lactated Ringers or Plasmalyte is preferred over normal saline because of lower risk of mortality and renal injury

• C.) Data is conflicting, but in the large scheme of things, probably doesn’t matter

• D.) Use of colloid based agents such as 4% albumin or hydroxyethyl starch is preferred in patients with septic shock
0.9% saline versus Balanced Crystalloids

• Choice of intravenous fluids in intensive care units has been shown to influence outcomes

• Historically 0.9% sodium chloride solution has been the most commonly used fluid in the ICUs
## Fluid comparisons

<table>
<thead>
<tr>
<th>Fluid composition</th>
<th>NS</th>
<th>LR</th>
<th>Plasmalyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na (mEq/L)</td>
<td>154</td>
<td>130</td>
<td>140</td>
</tr>
<tr>
<td>Cl (mEq/L)</td>
<td>154</td>
<td>109</td>
<td>98</td>
</tr>
<tr>
<td>K (mEq/L)</td>
<td>-</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Ca (mEq/L)</td>
<td>-</td>
<td>2.7</td>
<td>-</td>
</tr>
<tr>
<td>Mg (mEq/L)</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Buffer (mEq/L)</td>
<td>None</td>
<td>Lactate 28</td>
<td>Gluconate 23 Acetate 27</td>
</tr>
<tr>
<td>pH</td>
<td>5</td>
<td>6.5</td>
<td>7.4</td>
</tr>
<tr>
<td>SID</td>
<td>0</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Price/L</td>
<td>$1.30</td>
<td>$1.66</td>
<td>$7.12</td>
</tr>
</tbody>
</table>

Normal Saline versus Balanced Crystalloids

- Large pragmatic single center trial in 2018
  - ↓ mortality and ↓ renal injuries in patients who received balanced crystalloid than those with 0.9% saline

- Differences small
  - Prompted clinicians to change practice
  - LR> NS for resuscitation

Balanced Multielecctrolyte Solution versus Saline in Critically Ill Adults

Simon Finfer, M.D., Sharon Micallef, B.N., Naomi Hammond, Ph.D., Leanlove Navarra, B.S.N., Rinaldo Bellomo, M.D., Ph.D., Laurent Billot, M.Res., Anthony Delaney, M.D., Ph.D., Martin Gallagher, M.D., Ph.D., David Gattas, M.D., Qiang Li, M.Biostat., Diane Mackle, M.N., Jayanthi Mysore, M.S., et al., for the PLUS Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group

Abstract

BACKGROUND
Whether the use of balanced multielecctrolyte solution (BMES) in preference to 0.9% sodium chloride solution (saline) in critically ill patients reduces the risk of acute kidney injury or death is uncertain.
Normal Saline versus Balanced Crystalloid

- > 5000 critically ill patients who required fluid resuscitation to received normal saline or Plasmalyte (140 mEq of sodium and 98 mEq of chloride)

- Median volume administered was 3.8L

- Renal replacement therapy, organ failure, and mortality at 90 days were similar

Normal saline versus balanced solution

Weaknesses

• 63 % of Plasmalyte group received 500 ml or more of open-label saline group and 3.5 percent in the saline group received 500 ml or more of the Plasmalyte

• The investigators did not control or record all fluid that the patients received outside the ICU

• Traumatic brain injury patients were excluded because saline has been shown to be beneficial in these patients

Balanced Crystalloids versus Saline in Critically Ill Adults — A Systematic Review with Meta-Analysis

Naomi E. Hammond, Ph.D.¹,², Fernando G. Zampieri, Ph.D.³,⁴, Gian Luca Di Tanna, Ph.D.⁵, Tessa Garside, Ph.D.¹,², Derick Adigbi, Ph.D.¹,², Alexandre B. Cavalcanti, M.D. Ph.D.¹, Flavia R. Machado, M.D., Ph.D.⁶, Sharon Micallef, B.N.¹, John Myburgh, Ph.D.¹,⁷, Mahesh Ramanan, M.Med.⁸,⁹, Todd W. Rice, M.D.¹⁰, Matthew W. Semler, M.D.¹⁰, Paul J. Young, Ph.D.¹¹,¹², Balasubramanian Venkatesh, M.D.¹³, Simon Finfer, M.D.¹⁴, and Anthony Delaney, Ph.D.¹,²
Take home points

• Conflicting evidence exists regarding the choice of resuscitation fluid in the ICU setting

• It is likely that there is a small benefit of balanced solution over 0.9% saline in critically ill patients
  • Remains controversial

• Fluid choice can be individualized
  • Traumatic brain injury, metabolic alkalosis, hyponatremia
    • Saline preferred

40-year-old female with H/O IV Drug Abuse

Presents with cellulitis in the leg and MSSA bacteremia. She is a difficult stick and cannot maintain a functional peripheral IV.

What is the best choice for access?

• A.) Peripheral Inserted Central Catheter (PICC)
• B.) Midline Catheter
• C.) Internal Jugular Venous Line
• D.) Avoidance of any invasive catheters- use oral antibiotics
PICC versus midline catheters

- Midline catheters grown in popularity
  - Emphasis on ↓ central line associated bloodstream infections and deep venous thrombosis

- Previous studies → midlines less likely to cause complications

- But with ↑ use of midlines and more data
  - Concerns about complications (infection, thrombosis and failure) emerged
  - Newer observational studies → rival or outnumber complications from PICCs?

PICC versus Midline

PICC versus Midline Catheters

• Results cohort study published in November of 2021

• 10,863 patients with PICC or midline placed due to difficult venous access or intravenous antibiotic therapy for 30 or fewer days from 2017-2020

PICC versus Midline Catheters

• Results →→ patients who received PICCs had a greater risk of developing a major complication than those who received midlines

  – ↓ Catheter related bloodstream infections and catheter occlusions

  – Same rate of DVTs
    • Of note, some studies prior to this analysis showed midlines to have higher rates of thrombosis

6 Take Home points

• 1.) DOACs are preferred over LMWH for cancer related thrombosis
  • Apixaban should be preferred in intraluminal GI malignancies to reduce bleeding risk

• 2.) SGLT2 inhibitors reduce all cause cardiovascular mortality, hospital readmissions and quality of life scores across a broad range of patients with heart failure and should be added early on, irrespective of diabetes or background of other GDMT

• 3.) Newer contrast agents are generally safe in populations previously thought to be at risk for contrast induced nephropathy, and should not be withheld for fear of renal injury, especially if it will change management
6 Take home points

• 4.) Adherence to evidence based guidelines should be employed for secondary prevention of acute ischemic stroke

• 5.) Balanced solution versus saline remains controversial, but based on recent evidence, probably doesn’t a large effect on mortality and renal end points, but choice of fluids should be tailored to the specific clinical scenario

• 6.) Mid line catheters preferred for patients with difficult vascular access, for treatment that will likely exceed 6 days, and will require infusions up to 14 days
References
