



# Updates in Hospital Medicine: 2021-22

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# Updates in Hospital Medicine 2021-22

**No Conflicts of Interest**

# Updates in Hospital Medicine 2021-22

## Objectives

- Review and evaluate recent impactful literature in the practice of Hospital Medicine
- Develop a plan for how this data may: confirm, inform, or perhaps change your practice
- Save you some time and keep you entertained

# Updates in Hospital Medicine 2021

# Road Map

- New literature from 2021-22
  - High level review
    - Case based approach
  - Mix of Quick Takes/ Deep Dives
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- Articles selected based on likelihood to:
    - ✓ Change practice
    - ✓ Inform/Modify practice
    - ✓ Confirm practice



# Fluid: too much or not enough

56 yo F with a hx of RA and DM II p/w fever, dysuria, and flank pain for the last 2-3 days

- VS: T38.6, HR 112, BP 82/53, RR 21, SpO2 98% on RA
- Labs: WBC: 17.2, CMP wnl, Lactate 4.3,

Given 1.5L of IVF (~30cc/kg) in the ED with good response, IV CTX started and called to admit.

~2 hours later you are paged

- VS: T 38.1, HR 106, BP 85/48, RR 20, SpO2 99% on RA
- Labs: Lactate 2.8

# Fluid: too much or not enough

You re-examine the patients volume status (JVP, Legs, POCUS, Armpits) and she does not appear frankly hypervolemic. Do you?

- a) Give a 1L of LR because you're interested to see what those fluids the surgeons use are like
- b) Give 1 L of NS because its cheap, on hand, and you're a medicine doctor
- c) Call the ICU to start vasopressor support to avoid over-resuscitation
- d) Who knows, volume status and fluid resuscitation is all voodoo anyways

# Fluid: too much or not enough

## Background

- Observational studies and small RCT's have shown potential harm from too much IVF
- Recent Meta Analysis showed no mortality difference and that current evidence was questionable and of low quality<sup>1</sup>

<sup>1</sup>Meyhoff et al Chest 2020

# Restrictive Fluids in Shock

## Randomized Controlled Trial of Restrictive vs Standard IVF for Septic Shock

- 1554 pts, 31 ICUs, 8 European countries
- Inclusion: >18 yo, Septic Shock
- Exclusion: >12 hrs of shock, Major Hemorrhage, >10% BSA burn
- Followed for 90 days from randomization



# Restrictive Fluids in Shock

## Primary Outcome

- **All Cause Mortality**

## Secondary Outcomes

- Serious Adverse Event
  - Ischemia (Cerebral, Myocardial, Intestinal, Limb)
  - Severe AKI
- Serious Adverse Reaction
- Days alive without life support
- Days alive and OOH

# Restrictive Fluids in Shock

## Pre-Specified Sub-Groups

- Respiratory Support
  - NIVPP or Intubation
- Acute Kidney Injury
- Plasma Lactate >4
- Body Weight >76kg
- IV Fluid >30ml/kg within 24 hrs prior to randomization

# Restrictive Fluids in Shock

## Restrictive

- 4 reasons to give fluid (250-500 ml)
  - Severe hypoperfusion
    - Lactate >4
    - MAP < 50 mm on vasopressor/inotrope
    - Mottling above knee cap
    - Low UOP within 2 hrs of randomization
  - Replace documented fluid losses (e.g., gastrointestinal or drain losses).
  - Dehydration/electrolyte losses if PO contraindicated
  - Daily fluid intake <1L if PO contraindicated

## Standard

- 3 reasons to give fluid (any bolus)
  - Improvement of Hemodynamics (Surviving Sepsis Guidelines)
  - Replace Observed/Expected fluid losses
  - ICU protocol recommended mIVF

# Restrictive Fluids in Shock

## Restrictive

- N=770
- Day 1 mean: 1,024 ml
- Day 5 mean: 2,327 ml
- Protocol Violated
  - 162 patients (21.5%)

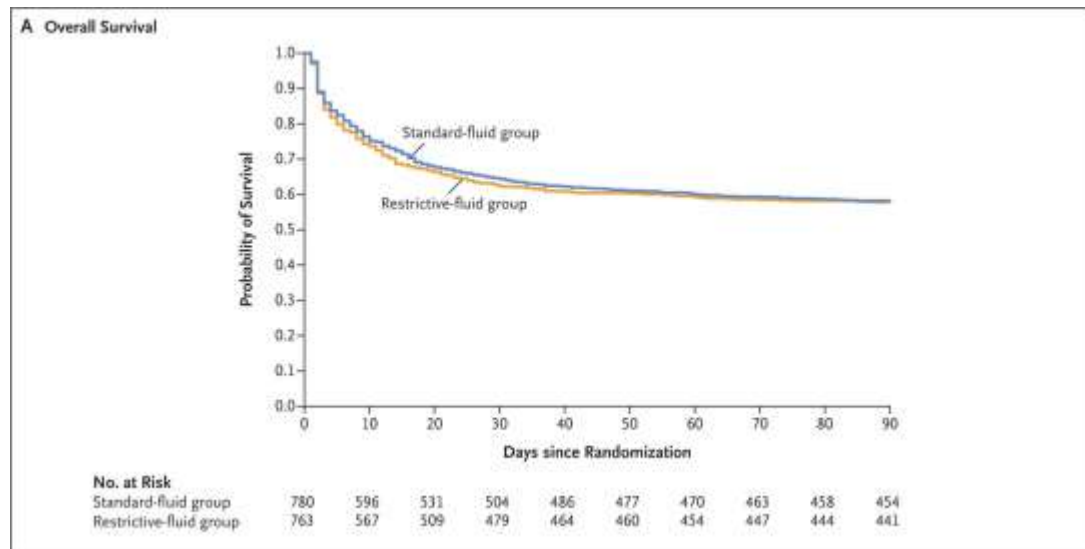
## Standard

- N=784
- Day 1 mean: 1724 ml
- Day 5 mean: 3836 ml
- Protocol Violated
  - 101 patients (13.0%)

# Restrictive Fluids in Shock

## Outcomes

- No difference in 90-day mortality
- No difference in any secondary outcome
- No difference among subgroups
  - Respiratory Support p of 0.03 (sig for heterogeneity is 0.01)



# Restrictive Fluids in Shock

- Caveats
  - ICU patients so not entirely generalizable
  - Limited ability account for effect of pre-ICU fluids
    - Less focus on initial resuscitation
- Takeaway
  - Adds to recent meta-analysis of RCT data showing no benefit for restrictive IVF

**Informs/Modifies** my practice towards being a bit less restrictive with IVF

# Fluid: too much or not enough

You re-examine the patient. She is clammy and toxic appearing but appears to be perfusing. You reassess her volume status (JVP, POCUS, Armpits) and she does not appear frankly hypervolemic. Do you?

- a) Give a 1L of LR because you're interested to see what those fluids the surgeons use are like
- b) Give 1 L of NS because its cheap, on hand, and you're a medicine doctor
- c) Call the ICU to start vasopressor support to avoid over-resuscitation
- d) Who knows, volume status and fluid resuscitation is all voodoo anyways

# OK now what fluid

## A brief preface

- Quick Take: Recent RCT of Normal Saline vs Balanced Crystalloid showing no benefit
- Deep Dive: Meta Analysis including this data showing likely benefit.



# Balanced vs Unbalanced IVF

## Double Blind, Randomized Controlled Trial of Balanced IVF vs Normal Saline in critically ill patients

- 5037 adult ICU pts, 53 ICUs, NZ and Australia
- 1:1 Randomization
- Inclusion: Adults >18 yo admitted to the ICU > 3days
- Exclusion: <500ml of IVF in ICU, imminent death or life expectancy <90 days
- Primary Outcome: **All Cause Mortality**
- Secondary Outcomes
  - Renal function: Peak Serum Creatine, Cr increase, new RRT
  - Pressor use
  - Mech Vent
  - ICU and Hosp LOS
- Followed for 90 days from randomization

# Balanced vs Unbalanced IVF

- Outcomes
  - No Difference found in Primary or Secondary Outcomes
  - No Differences in Subgroup Analysis

# Time to get META



# Time to get META

- Random Effects Model Metanalysis of RCT/Cluster RCTs of Balanced IVF (LR or Plasmalyte) vs Normal Saline
  - 13 trials identified (35,884)
  - 6 trials considered low risk of bias (34,450 participants)
  - Standardized Protocol for Secondary Analysis
    - Access to data from authors (no imputation of data)

# Time to get META

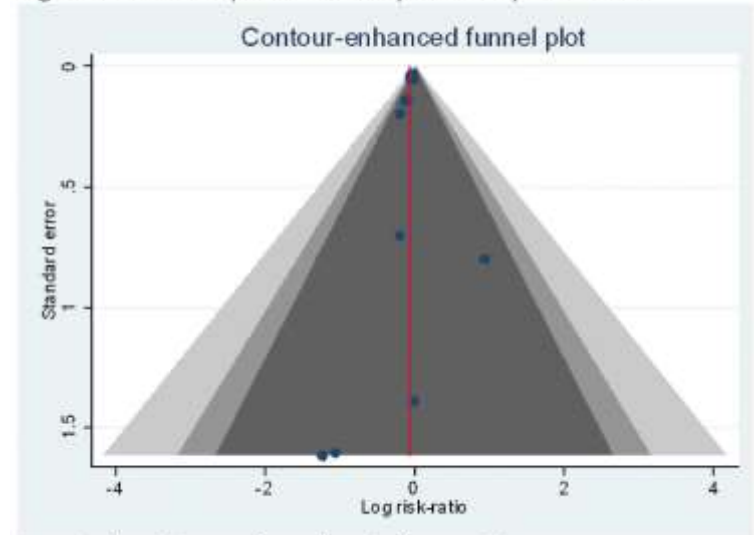
- Primary Outcome
  - All-Cause Mortality at 90 days
- Secondary Outcomes
  - AKI
  - Mortality (if 90 day not available)
  - CRRT incidence
  - Vent free days
  - Vasopressor Free Days
- Subgroups
  - Sepsis
  - TBI
  - Trauma
  - Cardiac Surgery

# Time to get META

- Primary Outcome
  - Relative Risk All-Cause Mortality
    - 0.96 (95% CI, 0.91-1.01)

## Funnel Plot

Figure S4: Funnel plot for 90-day mortality – All trials



Regression-based Egger test for small-study effects:  $p=0.79$

# Time to get META

## Secondary/Subgroup Outcomes

Outcome	Trials (n)	Participants (n)	Mean (SD)	Mean (SD)	Effect measure (95% CI)	95% CI	P
Secondary outcomes							
Treated with renal replacement therapy	5	33,554	0.02	59.5	0.95	0.81 to 1.11	
Incidence of acute kidney injury	5	25,224	0.00	8.6	0.96	0.89 to 1.02	
Ventilator-free days (to day 28)	5	32,191	0.32	79.5	0.18 <sup>§</sup>	−0.45 to 0.81	
Vasopressor-free days (to day 28)	3	21,622	0.02	24.1	0.19 <sup>§</sup>	−0.13 to 0.51	
Patient-level subgroup analysis for the primary outcome							
Sepsis	5	6,754	0.001	22.3	0.93	0.86 to 1.01	
Traumatic brain injury	3	1,896	0.01	20.2	1.26	0.98 to 1.60	
Trauma	4	3,863	0.03	16.5	0.99	0.70 to 1.39	
Cardiac surgery	3	2,420	0.01	7.6	1.13	0.76 to 1.69	
Cluster crossover	4	19,128	0.04	68.4	0.91	0.71 to 1.17	0.80
Individual patient randomly assigned	7	15,752	0.07	87.1	0.96	0.70 to 1.31	
Plasma-Lyte 148	5	17,785	0.16	95.8	0.99	0.64 to 1.54	0.74
Other/mixed balanced fluids	6	17,095	0.01	23.4	0.91	0.77 to 1.08	
All fluids	8	34,627	0.07	92.2	0.96	0.76 to 1.20	0.53
Resuscitation fluids only	5	253	0.02	4.6	0.81	0.52 to 1.27	

# Balanced vs Unbalanced Fluids

- Caveats
  - ICU patients → Generalizable?
  - CI ranges from 9% chance of mortality reduction to 1% chance of harm
- Takeaways
  - Far greater likelihood of harm than benefit of NS
    - Effect size is not large

**Confirms** my practice of using Balanced Crystalloid over Normal Saline unless clinically indicated



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# Safe with the Slide

56 yo F with a hx of RA and DM II a/w sepsis now improving. In the light of day you wonder what to do with her DM regimen.

Overnight she was started on Sliding Scale Insulin with her home Metformin, Glipizide, and Sitagliptin (Januvia) held. Admission Glucose was 138 and her current BG is 156. She has received 3 units of insulin aspart overnight.

Do you?

- a) Transition her to a Basal Bolus Insulin regimen based on current insulin use
- b) Restart her home Metformin, Glipizide, beg Rx to allow Sitagliptin and stop all insulin
- c) Start an Insulin gtt so you have a better sense of her insulin needs
- d) Sit pat and see how SSI does during the stay

# Safe with the Slide

## Background

- Multiple Studies show improved glycemic control of Basal/Bolus when compared to SSI
- Single study found improved peri-operative complications with Basal/Bolus
- American College of Endocrinology, American Diabetes Association, and Endocrine Society guidelines all recommend Basal Bolus therapy for non-critical inpatient care.

~40% of IP with hyperglycemia are still treated with SSI alone<sup>1</sup>

# Safe with the Slide

## Retrospective cohort study of SSI use in inpatients with Type 2 DM

- Inclusion Criteria: Adult non-critical inpatients with T2D
  - 25,813 total patients
    - 16,366 received SSI during their hospitalization
    - Exclusion: any ICU stay, IV insulin, missing BG data, Index BG >500, LOS <1 day, received Basal Insulin within first 2 days of stay, or patients who were treated with oral/injectable antidiabetic meds

# Safe with the Slide

8095 (31.4%) received SSI Monotherapy

- 1,192 (15%) were transitioned to Basal insulin after day 2
- 6903 (85%) remained on SSI throughout

Those transitioned tended to be

- Younger
- Non-white race
- Surgical Patients
- Higher admission BG
- Higher HgbA1c
- Higher rates of CKD
- Higher Charlson Comorbidity Index

# Safe with the Slide

## Primary Outcome

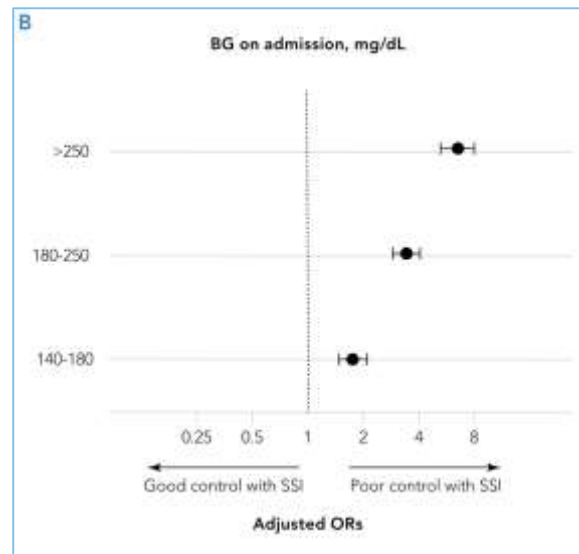
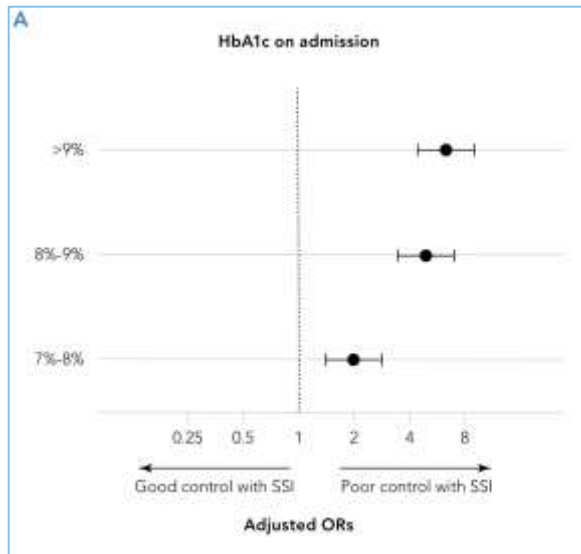
- Mean Hospitalization BG <180
  - **96%** of patients with Admission BG <140
  - **83%** for patients with admission BG 140-180
  - **15%** for patient with admission BG >250
  - **53%** of Basal Bolus achieved mean BG <180
    - **88.5%** of those with Admission BG 140-180 met goal

## Hypoglycemia

- **8%** in SSI vs **18%** in Basal Bolus

# Safe with the Slide

Multivariate Logistic Regression controlling for factors which predicted transition to Basal Insulin found...



# Safe with the Slide

## Caveats

- High risk of bias by indication/selection
- Basal/Bolus were clearly sicker

## Take Aways

- Does not support idea that SSI is non-inferior to Basal/Bolus
- Does identify patients for whom a less intensive approach is the least likely to cause harm.

**Informs/Modifies** my practice to focus efforts to transition SSI to Basal Bolus based on admission glucose and HgbA1c



# Safe with the Slide

56 yo F with a hx of RA and DM II a/w sepsis now improving. In the light of day you wonder what to do with her DM regimen.

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- c) Start an Insulin gtt so you have a better sense of her insulin needs
- d) **Sit pat and see how SSI does during the stay**

# ESBL on DC

56 yo F with a hx of RA and DM II p/w fever, flank pain, and dysuria fth Sepsis 2/2 UTI now HD 4 ready for discharge.

Her Urine Culture unfortunately has returned with Klebsiella only sensitive to Pip-tazo and Ertapenem

- a) Call ID and Case Management to start planning OP IV Antibiotics
- b) Keep her inpatient for a few extra days to finish a short course
- c) Try Fosfomycin PO once every other day for 7 days
- d) Call in some favors and prescribe Terbipenem on her way out the door

# ESBL on DC

## Current State

- Complicated UTI's with Quinolone and TMP/SMX resistance often require extended courses of IV Ertapenem to complete a full course
- Deeper Dive: Off-label PO Fosfomycin
- Quick Take: Oral Carbapenem RCT

# ESBL in cUTI

## Multicenter Retrospective Cohort study of Fosfomycin vs Ertapenem for treatment of cUTI

- 3 Public Hospitals in Los Angeles Area (2018-2020)
- 322 total cases of cUTI
  - 110 in Fosfomycin arm
  - 212 in Ertapenem control arm
- Primary Outcome: Resolution of Symptoms @ 30 days

# ESBL in cUTI

## Inclusion Criteria:

- All complicated UTIs treated with Fosfomycin or Ertapenem
  - cUTI: + UCx, Symptoms and Complicated Findings
    - Indwelling Catheter, Renal Stone, Obstruction, Ureteral Stent, Transplant
    - Flank pain w/ fever or leukocytosis

## Exclusion:

- Prostatitis
- Asymptomatic Bacteremia
- Uncomplicated Cystitis
- Epididymo-orchitis
- Non-UTI Infections

# ESBL in cUTI

- Abx adjudicated based on final Abx received
  - Previous alternative IV therapy allowed
  - Fosfomycin
    - 3 dosing intervals
      - Daily (n=29), Every Other day (n=59), Every Third Day (n=22)
  - Ertapenem
    - OP vs IP Daily IV infusion

# ESBL in cUTI

- Ertapenem Arm
  - 91.0% Ucx had ESBL
- Fosfomycin Arm
  - 84.6% of Ucx had ESBL
  - Higher rates of TMP/SMX resistance

	Fosfomycin (n = 110)	Ertapenem (n = 212)	PValue
cUTI type			
Bladder catheter at diagnosis	27 (24)	31 (15)	.03
Pyelonephritis, no PCNT	48 (44)	139 (66)	<.001
PCNT	15 (14)	32 (15)	.7
Cystitis with nephrolithiasis	5 (5)	1 (<1)	.02
Other urinary obstruction <sup>a</sup>	11 (10)	5 (2)	.004
Other cUTI <sup>b</sup>	4 (4)	4 (2)	.3
Comorbidities			
Diabetes mellitus	48 (43.6)	99 (46.7)	.6
Urinary obstruction	55 (50.0)	93 (44)	.3
Renal abscess	2 (1.8)	7 (3.3)	.4
Nephrolithiasis (all cUTI types)	25 (22.7)	35 (16.5)	.1
Bacteremia	7 (6.4)	82 (38.7)	<.0001
Bladder catheter at discharge	31 (28.2)	40 (18.9)	.06
Renal transplant	0 (0)	7 (3.3)	.05

# ESBL in cUTI

## Primary Outcome: 30 day Clinical Success

- 72/110 [65.4%] vs 157/212 [74.1%];  $P = .10$

## Secondary Outcomes

- No difference in symptoms resolution at last F/u or relapse rate
- No difference in Fosfomycin Success by
  - No IV lead in (n=15), IV therapy 1-3 days (n=38), 4-5 days (n=44), >6 days (n=13)



# ESBL in cUTI

## Adjusted Analysis

- 30 day Resolution of Symptoms: **1.21 (95% CI, 0.68–2.16)**
- Resolution at last follow up: **0.84 (95% CI, 0.46–1.52)**
- Relapse: **0.94 (95% CI, 0.52–1.70)**

**Adverse Events:** 1 vs 10 (p=0.06),

**Hospital Length of Stay:** 1.4 days shorter

**Duration of Therapy:** 3.8 days shorter

**IV Therapy:** ~10.5 days shorter

# ESBL in cUTI

## Caveats

- Retrospective Analysis → High risk of bias by indication
  - Ertapenem Pop → Sicker, more bacteremia/pyelo
  - Fosfomycin Pop → More indwelling catheters (higher failure rate)

# Quick Take: PO Penem?

Large, Non-Inferiority Double Blind RCT of PO Tebipenem vs IV Ertapenem for treatment of cUTI.

1372 Hospitalized Adults, 1:1 randomization  
Tx Course: 7-10 days (14 days if bacteremia)

Primary Outcome: Test of Cure Visit (~Day 19)  
- Composite of Clinical Cure and Microbiological Response

Secondary Outcome: Overall response at end of treatment

# Quick Take: PO Penem?

## Primary Outcome: Test of Cure Visit

- 58.8% Tebipenem vs 61.6% Ertapenem (95% CI -9.7-3.2% diff)
  - NI threshold was 12.5%

## Secondary Outcome: Overall Response/Clinical Cure

- 97.3% Tebipenem and 94.5 Ertapenem

## Adverse Events/Safety

- Any AE: Tebipenem 25.7% vs Ertapenem 25.6
- Severe AE: 1.5 Tebipenem vs 1.3 Ertapenem with no difference between drugs

# ESBL in cUTI

## Takeaways

- If you have access, use Tebipenem
- If you don't, Fosfomycin may be a reasonable off-label substitute in low risk patients
  - Reasonable to await an RCT

**Changes** my practice to consider alternative PO options (Tebipenem > Fosfomycin) for ESBL cUTI treatment

# ESBL on DC

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Her Urine Culture unfortunately has returned with Klebsiella only sensitive to Pip-tazo and Ertapenem

- a) **Call ID and Case Management to start planning OP IV Antibiotics**
- b) Keep her inpatient for a few extra days to finish a short course
- c) **Try Fosfomycin PO once every other day for 7 days**
- d) **Call in some favors and prescribe Tebipenem on her way out the door**

Thank You!