Adam Thomas Hussein Kanji

Critical Care BC Connect Update - May 2023

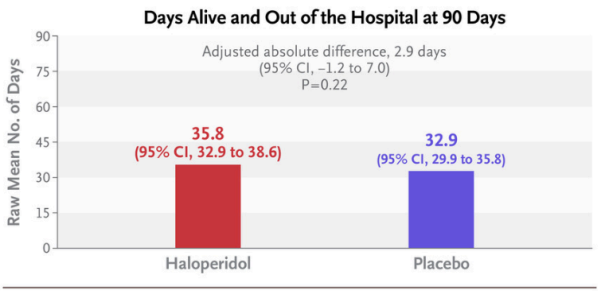
Sedation / Delirium

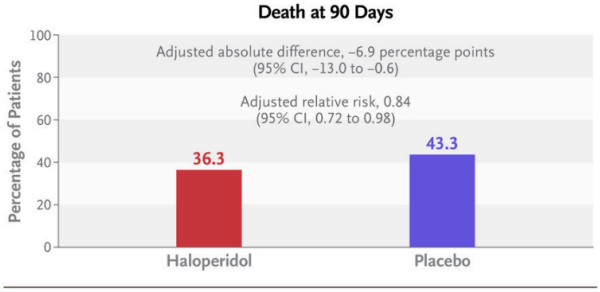
Regular Haldol likely not saving lives

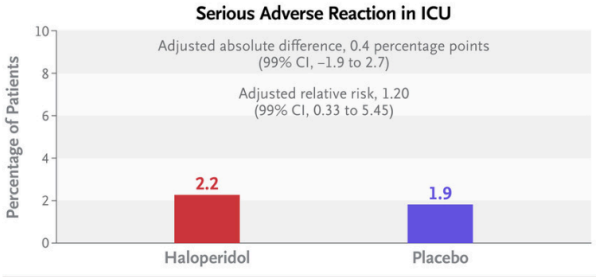
In this nice multi-centre RCT out of Europe published in NEJM: AID Trial looked at Haldol for a mixed ICU population with delirium showed NO BENEFIT to TID haloperidol versus placebo.

Context: Prior Studies (HOPE-ICU & MIND-USA) showed that prophylactic and regular antipsychotics in predominately hypoactive delirium did not help patients. In this population with a mix between hypo and hyperactive, there was still no clinical benefit, but interesting signal of benefit?

Bottom line: use of haldol should be limited to HYPERactive delirium.
Summary Here



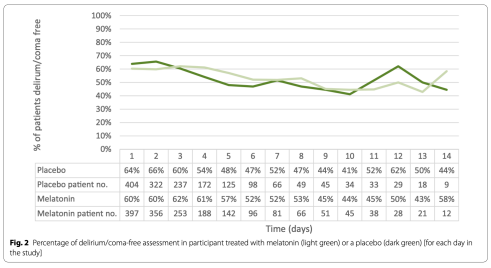




The fall of melatonin in ICU

In this Australian multi-centre RCT, the Pro-MEDIC trial compared Prophylactic Melatonin to placebo for improvement sin daily delirium assessments. There was NO BENEFIT to initiating enteral melatonin on admission to ICU.

Context: a prior small single centre RCT showed potential decrease LOS in ICU and improved sleep. This benefit was not demonstrated in this trial. LOS and sleep quality had no difference here.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Placebo	64%	66%	60%	54%	48%	47%	52%	47%	44%	41%	52%	62%	50%	44%
Placebo patient no.	404	322	237	172	125	98	66	49	45	34	33	29	18	9
Melatonin	60%	60%	62%	61%	57%	52%	52%	53%	45%	44%	45%	50%	43%	58%
Melatonin patient no.	397	356	253	188	142	96	81	66	51	45	38	28	21	12

Fig. 2 Percentage of delirium/coma-free assessment in participant treated with melatonin (light green) or a placebo (dark green) (for each day in the study)

Bottom line: Melatonin probably does not belong on everyone's MAR / admission order-set
Summary Here

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Respiratory Support

Table 3. Outcomes of Tracheal Intubation

	Fluid bolus (n = 538)	No fluid bolus (n = 527)	Difference (95% CI)[a]
Primary outcome			
Cardiovascular collapse, No. (%)[b]	113 (21.0)	96 (18.2)	Absolute, 2.8 (−2.2 to 7.7)
New or increased receipt of vasopressors	111 (20.6)	93 (17.6)	Absolute, 3.0 (−1.9 to 7.9)
Systolic blood pressure <65 mm Hg[c]	(n = 535) 21 (3.9)	(n = 524) 22 (4.2)	Absolute, −0.3 (−2.8 to 2.3)
Cardiac arrest	9 (1.7)	8 (1.5)	Absolute, 0.2 (−1.5 to 1.8)
Death	4 (0.7)	3 (0.6)	Absolute, 0.2 (−1.0 to 1.3)
Secondary outcome			
In-hospital death prior to 28 d, No. (%)	218 (40.5)	223 (42.3)	Absolute, −1.8 (−7.9 to 4.3)
Exploratory procedural outcomes[d]			
Systolic blood pressure, median (IQR), mm Hg[c]			
Lowest level	116 (93 to 139)	113 (95 to 134)	Median, 3.0 (−3.0 to 7.0)
Change in level	−7 (−26 to 0)	−9 (−27 to 0)	Median, 2.0 (−2.0 to 5.0)
Lowest arterial oxygen saturation, median (IQR), mm Hg	96 (86 to 100)	96 (88 to 100)	Median, 0 (−2.0 to 1.0)
Oxygen saturation <80%, No. (%)	(n = 531) 79 (14.9)	(n = 518) 71 (13.7)	Absolute, 1.2 (−3.3 to 5.6)
Exploratory clinical outcomes, median (IQR)			
Invasive mechanical ventilation-free days through 28 d[e]	14 (0 to 25)	12 (0 to 25)	Median, 2.0 (−10.0 to 15.0)
Intensive care unit-free days through 28 d[f]	9 (0 to 22)	9 (0 to 22)	Median, −0.5 (−9.0 to 9.5)

If you give a drug to drop SVR, Fluids won't help alone

In this follow up RCT, the PRE-PARE II trial published in JAMA explored fluid administration and peri intubation hypotension / cardiovascular collapse.

Context: Peri intubation is brought with cardiovascular collapse in our critically ill patients. The prior PREPARE 1 trial showed no benefit to fluid administration apart from those patients getting positive pressure ventilation.

Bottom Line: I will continue to be using in line vasopressors for all critically ill intubations, as 1/5 patients will experience a SBP <65 or need higher doses of pressers, whether 500ml of crystalloid is given or not.

Summary here

Aim for the mid-field in SPO2 targets for N/IMV Patients

In this single centre crossover RCT (Nashville PILOT Trial) there was no clinical benefit to low (88-92%) vs intermediate (92-96%) or vs high (96-100%) SPO2 targets.

Context: After the ICUROX challenged how we target O2 sats, this small but well done trial confirms the goldilocks principle, no need to go too low or too high until MEGA-ROX guides us more.

Bottom line: no need to set an aggressively low or high O2 target, I'll aim for the middle of the field (92-96%)

Summary Here

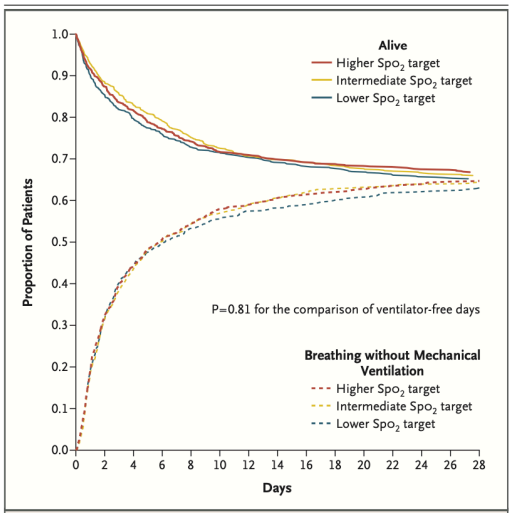

Figure 2. Proportion of Patients Alive and Not Receiving Invasive Mechanical Ventilation.

The proportion of patients who were alive and breathing without invasive mechanical ventilation during the 28 days after enrollment in each Spo_2-target group is shown. In a proportional-odds model, the number of days that patients were alive and free of invasive mechanical ventilation through day 28 did not differ significantly among the groups (P=0.81).

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IDSA in 2018 was right, Steroids in severe community Acquired Pneumonia

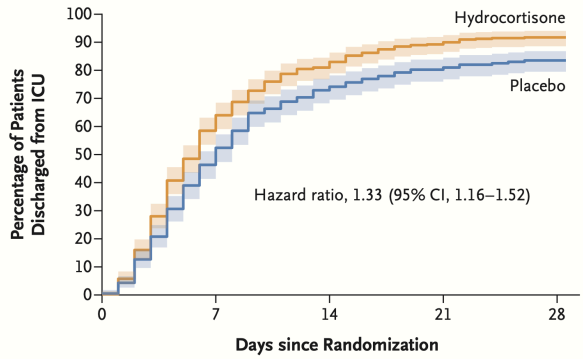

Figure 2. Discharge from ICU by Day 28.
Shown is the cumulative percentage of patients who were discharged from the ICU by day 28 (a secondary outcome in the trial). The length of ICU stay was compared in the framework of a competing-risk model, with death considered as a competing event. For secondary outcomes, the widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

In the CAPE-COD multi centre RCT published in NEJM, the early use of hydrocortisone (200mg administered over 24hr infusion) for 4 days lowered 28 day mortality in this admitted to ICU with severe CAP.

Context: Prior to the DEXA-ARDS trial, it was unclear who to administer steroids to with severe community acquired pneumonia. In the post covid era steroids are more readily administered, but over the past 25 years the evidence for the used of steroids in severe CAP was the ultimate pendulum.

Bottom line: Its appears for our CAP patients who are severely inflammatory phenotype (here a CRP >150) they would benefit from the administration of early steroids when admitted to ICU. Summary Here

BMI >35? Extubate to NIV

In this French multi centre RCT, the EXTUB-OBESE trial showed that extubation to NIV reduced the need for re-intubation / change of study therapy or stopping study therapy in obese critically ill patients.

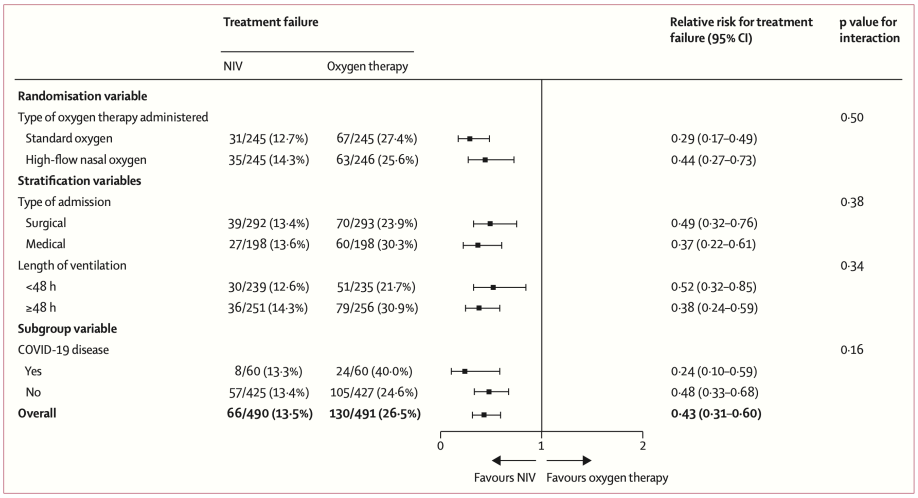

Figure 2: **Subgroup analyses of the primary outcome**
None of the prespecified characteristics, including length of mechanical ventilation, type of admission, or SARS-CoV-2 infection appeared to modify the effect of NIV group on the treatment failure rate. NIV=non-invasive ventilation.

Context: Although clinical guidelines and expert opinion still recommend extubation to NIV, some growing discussion around using HFNC for all extubations are creating into our practise.

Bottom Line: Our obese patients should be extubated to NIV and not other oxygen therapies alone.

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Deep sedation is harming our patients

In this mammoth of an international multi-centre observation trial, aka WEAN SAFE, a sobering result was that patients that are unable to wean from the ventilator quickly are likely to have a bad outcome. Sedation appears to be on low hanging fruit that can impact this patient population greatly. Factors of note: Frailty, Trauma, Use of NMBA, Mod/Deep sedation, increasing age, immunocompromised, cardiac arrest.

Interesting, only 65% of patients who are vented beyond 48hrs will be successfully weaned by 90 days post ventilation. Sedation seemed to prolong time to wean trial, as did lack of spent breathing trials.

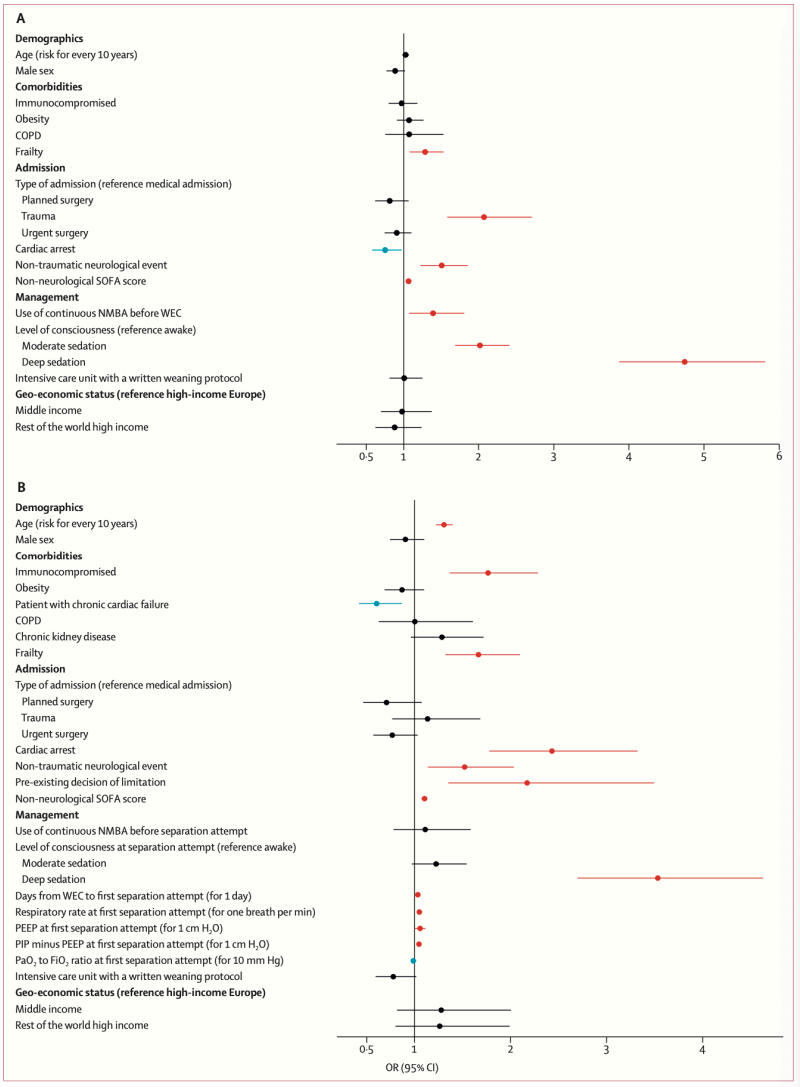

Figure 4: **Risk factors for weaning delays and weaning failure**
(A) Multilevel multivariable analyses showing the association between variables retained in the models and delayed initiation of weaning (ORs [95% CIs]). Blue dots and whiskers show variables significantly associated with lower risk of delayed initiation of weaning. Red dots and whiskers show variables associated with increased risk of delayed initiation of weaning. Black dots and whiskers show non-statistically significant ORs and 95% CIs. (B) Multilevel multivariable analyses showing the association between variables retained in the models and failed weaning. Blue dots and whiskers show variables significantly associated with lower risk of failed weaning (ORs [95% CIs]). Red dots and whiskers show variables associated with increased risk of failed weaning. Black dots and whiskers show non-statistically significant ORs and 95% CIs. COPD=chronic obstructive pulmonary disease. NMBA=neuromuscular blocking agents. OR=odds ratio. PEEP=positive end-expiratory pressure. PIP=peak inspiratory pressure. SOFA=Sequential Organ Failure Assessment. Pre-existing decision of limitation=decision to withhold or withdraw life sustaining treatments before intensive care unit admission. WEC=weaning eligibility criteria.

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Fluids

Early vasopressors or less fluids in septic shock?

In the last year we saw both the CLOVERS and CLASSIC trials come out.

In the CLOVERS trial we see a multi-centre RCT of restrictive fluid (limit crystalloids, start vasopressors early) versus liberal fluid arm (bolus fluids before starting vasopressors). There was no difference in either group, apart from the fluid received (1.2L vs 3.8L in 24hrs).

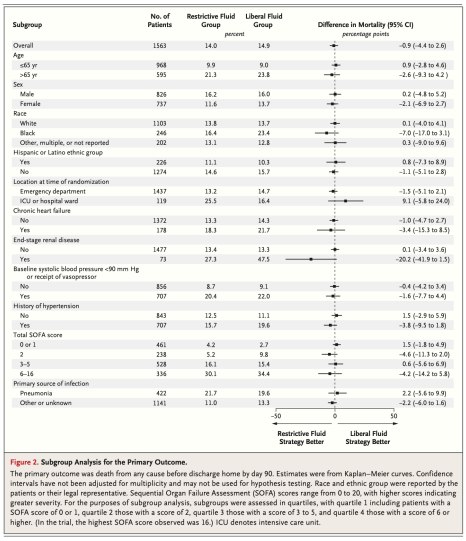

Figure 2. Subgroup Analysis for the Primary Outcome.

The primary outcome was death from any cause before discharge home by day 90. Estimates were from Kaplan–Meier curves. Confidence intervals have not been adjusted for multiplicity and may not be used for hypothesis testing. Race and ethnic group were reported by the patients or their legal representative. Sequential Organ Failure Assessment (SOFA) scores range from 0 to 20, with higher scores indicating greater severity. For the purposes of subgroup analysis, subgroups were assessed in quartiles, with quartile 1 including patients with a SOFA score of 0 or 1, quartile 2 those with a score of 2, quartile 3 those with a score of 3 to 5, and quartile 4 those with a score of 6 or higher. (In the trial, the highest SOFA score observed was 16.) ICU denotes intensive care unit.

Table 3. Outcomes.*

Outcome	Restrictive Fluid Group (N=782)		Liberal Fluid Group (N=781)		Difference (95% CI)†
	No. of Patients	Mean (95% CI)	No. of Patients	Mean (95% CI)	
Death before discharge home by day 90 — % of patients‡	782	14.0 (11.6 to 16.4)	781	14.9 (12.4 to 17.4)	−0.9 (−4.4 to 2.6)§
No. of days free from organ-support therapy at 28 days	778	24.0 (23.4 to 24.6)	778	23.6 (23.0 to 24.3)	0.3 (−0.5 to 1.2)
No. of days free from ventilator use at 28 days	773	23.4 (22.7 to 24.1)	771	22.8 (22.0 to 23.5)	0.6 (−0.4 to 1.6)

Summary Here

In the CLASSIC trial, a restricted fluid approach (1.8L) vs standard fluid (3.8L) showed no change in clinical outcomes of importance.

Table 3. Primary and Secondary Outcomes.

Outcome	Restrictive-Fluid Group	Standard-Fluid Group	Adjusted Absolute Difference	Adjusted Relative Risk	P Value
			percentage points		
Primary outcome*					
Death by day 90 — no./total no. (%)†	323/764 (42.3)	329/781 (42.1)	0.1 (95% CI, −4.7 to 4.9)	1.00 (95% CI, 0.89 to 1.13)	0.96

It appears that after 15 years since PROMISE / ARISE / PROCESS, we are likely seeing multi-modal resuscitative efforts tailored to our patients needs.

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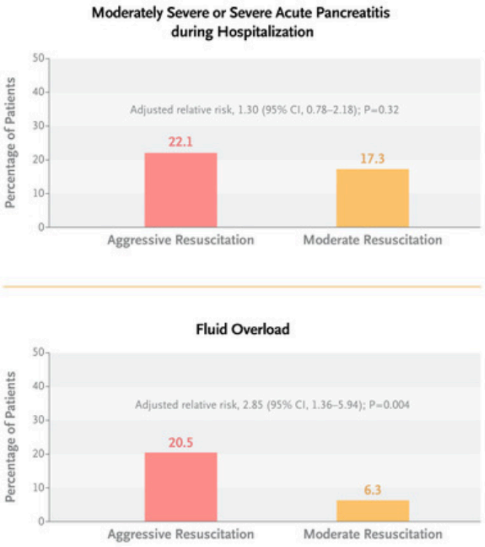
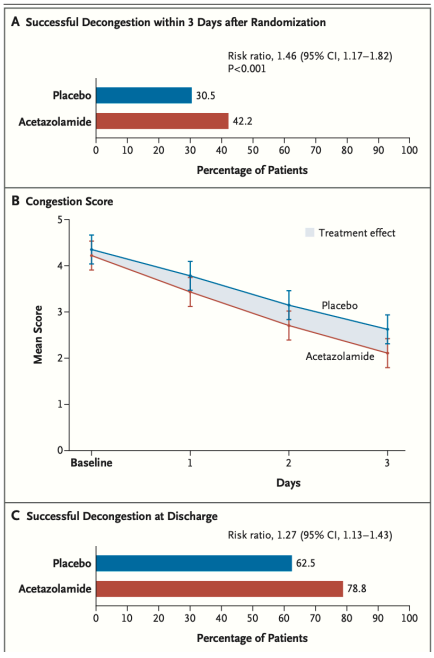


We need to stop drowning our pancreatitis patients

20 years in the works, a group was finally able to perform the [WATERFALL Trial](). This multi centre RCT of aggressive (20ml /kg bolus w/ 3ml/kg/hr infusion) vs moderate (10ml/kg bolus w/ 1.5 ml/kg/hr infusion) of ringer's lactate resuscitation in pancreatitis patients. No big differences apart from fluid overload, but the trial was stopped early due to safety concerns by DSMB.
[Summary here]()

Table 2. Primary and Secondary Outcomes.*

Outcome	Aggressive Fluid Resuscitation (N=122)	Moderate Fluid Resuscitation (N=127)	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)	No. of Patients with Missing Data†
Primary outcome: moderately severe or severe pancreatitis — no. (%)‡	27 (22.1)	22 (17.3)	1.28 (0.77–2.12)	1.30 (0.78–2.18)	0
Severe pancreatitis — no. (%)	8 (6.6)	2 (1.6)	4.16 (0.90–19.22)	2.69 (0.56–12.88)	0
Local complications — no. (%)					
Any complication	25 (20.5)	21 (16.5)	1.24 (0.73–2.09)	1.28 (0.74–2.22)	0
Necrotizing pancreatitis§	17 (13.9)	9 (7.1)	1.97 (0.91–4.24)	1.95 (0.87–4.38)	0
Infected necrotizing pancreatitis	5 (4.1)	3 (2.4)	1.74 (0.42–7.10)	1.45 (0.38–5.49)	0



Add acetazolamide to your diuresis regimes in CHF patients

In this multi-centre RCT, [ADVOR](), adding low dose acetazolamide (500mg daily) to standard loop diueresis resulted in faster time to decongestion and higher fluid negative levels obtained.

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Common Interventions

1. In this nice RCT clinical description in CHEST. Basically, a comparison of salvage epinephrine was equivalent to TXA in bleeding during bronchoscopy. TXA = Epi for bleeding after bronchoscopy.

2. In this French multi-centre RCT, stoping feeds then suctioning the stomach at the time of extubation was similar to 6 hrs of fasting. No need to holds feeds.

3. The TEAM Trial showed Early Active mobilization during IMV to be potentially HARMFUL Summary Here

4. The EFFORT trial showed high protein diet in critical illness should be avoided at least in AKI patients, and not needed for all patients. Nice Summary here

5. In this wild multi-centre RCT, patients with thrombocytopenia with counts 10,000- 50,000, likely need pre procedure transfusion IF YOU PLACE PREDOMINATELY SUBCLAVIAN LINES.