UPDATE IN HOSPITAL MEDICINE

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HOSPITALIST, MARTIN HEALTH SYSTEM & ADVENTIST HEALTH

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PGA NATIONAL RESORT & SPA

PALM BEACH GARDENS, FL

DISCLOSURE OF FINANCIAL RELATIONSHIPS

Ankush K Bansal

Has disclosed relationships with an entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients.

- Hospitalist Employment: **Hospitalists Plus, Martin Health System**
- Telemedicine Independent Contractor: HealthTap, WellnessFX, WellVia Solutions, American Well, Video Medicine

Case 1

A 60 year-old male presents to the emergency department with severe headache that started 2.5 hours ago. He has prior history of resistant Stage 2 to 3 hypertension (average 180/105) despite diuretic, beta blocker, adenosine-receptor blocker, and vasodilator therapy. He also has non-familial hyperlipidemia and diabetes mellitus type 2 with last A1c of 7.5%. Initial evaluation shows a blood pressure of 210/130, pulse of 90, afebrile status, and saturation of 93% on 2 L/min oxygen (89% on room air). His Glasgow Coma Scale is 15 and NIH Stroke Scale of 9 (0-40). CT head shows a 10 cc hematoma in the left basal ganglia but without intraventricular hemorrhage. Neurosurgery is consulted and they recommend admission to medicine with blood pressure control with consultation to them. You, the hospitalist, are called to admit this patient. You admit the patient to the ICU and order nicardipine at 5 mg/hour with increase by 2.5 mg/hour q15 min to a maximum of 15 mg/hour. You wonder what should be your goal blood pressure and how aggressive you should be.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage

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National Institute of Neurological Disorders and Stroke and the National Cerebral and Cardiovascular Center; ATACH-2 ClinicalTrials.gov number, NCT01176565.)

Introduction

Limited data on what the blood pressure goal should be for an acute hypertensive event in ICH

Point of reducing blood pressure is to limit hematoma expansion

Recent pilot study data suggested hematoma expansion was just as prevalent at 3-4.5 hours as 0-3 hours

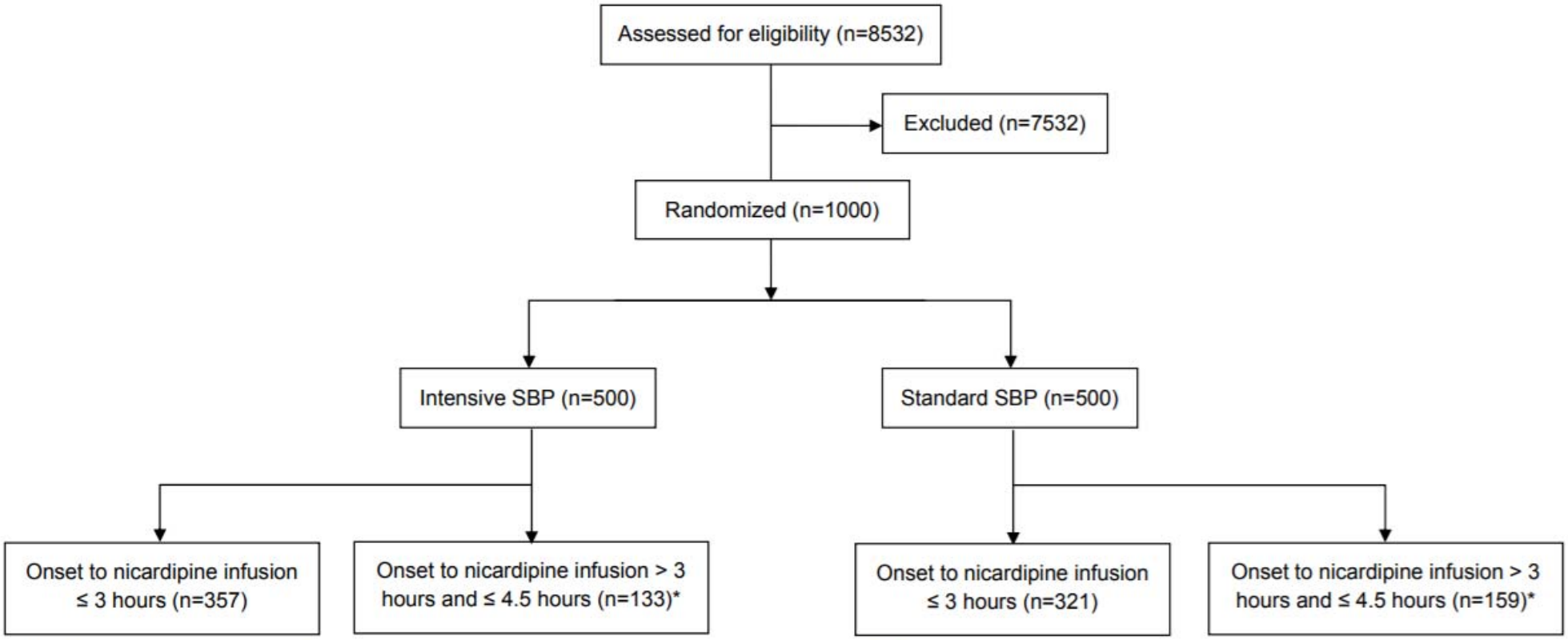
Study Design

- ATACH-2 trial – Antihypertensive Treatment of Acute Cerebral Hemorrhage II

- Goal: **For ICH <60 cc and GCS ≥5, does rapidly reducing blood pressure to SBP 110-139 vs 140-179 within 4.5 hours of symptom onset & continued hourly for 24 hours improve death and disability?**

- Multi-center, open-label, randomized controlled, intention to treat
- Adults aged ≥18 with ICH, at least one SBP ≥180, not reduced to <140 systolic prior to randomization
- 110 hospitals in USA, Japan, China, Taiwan, South Korea, and Germany (incl. Mayo, TGH, UFL_G)
- Conducted May 2011 to September 2015 (4.3 years)
- Screened 8532 then randomization (1000) of those with mean SBP 200 to:
  - Intensive group (500) – goal SBP 110-139
  - Standard group (500) – goal SBP 140-179
- Nicardipine within 4.5 hours of symptom onset – 5 mg/h, ↑ by 2.5 mg/h q15 min, max 15 mg/h with 2nd agent (if not at goal) of Labetalol (or diltiazem if Labetalol not available in that country)
- Blinded radiologist reads CT at initial presentation and at 24 hours to evaluate ACH expansion
- Serious AEs reported for 3 months
- "Non-serious" AEs reported for 7 days or until hospital discharge (earliest)
- Follow ups: 1 month by phone and 3 months by blinded in-person clinician

Supplementary Figure 1, The CONSORT Flow diagram to demonstrate progress through the phases of the trial



*10 subjects in intensive group and 20 in standard group have time from onset to nicardipine infusion longer than 4.5 hours

Outcomes

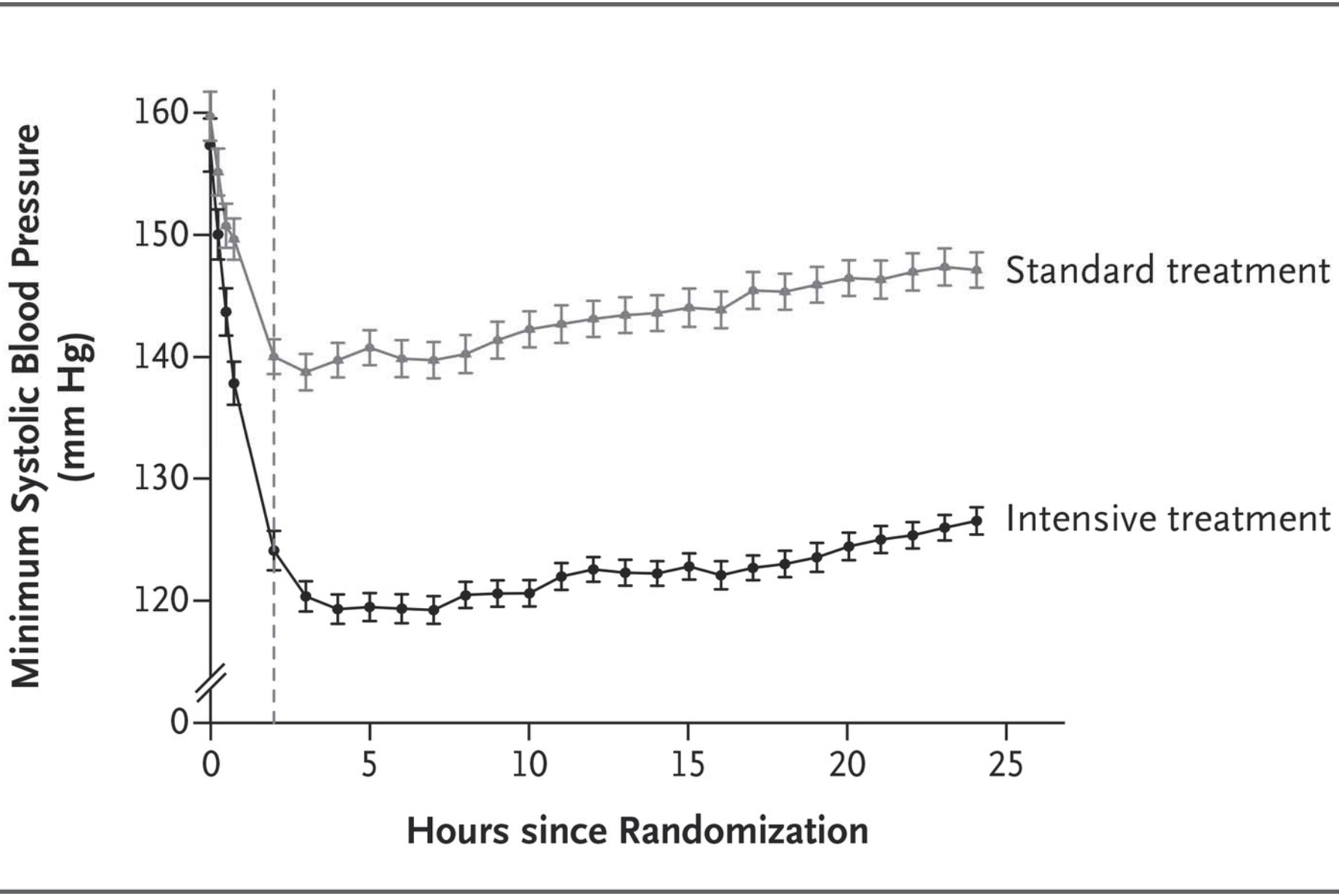
- Primary: Death or moderate to severe disability (modified Rankin score 4-6) at 3 months
- Secondary:
  - Quality of Life (EQ-5D) and perception of own health (VAS) at 3 months
    - EQ-5D: mobility, self-care, usual activities, pain/discomfort, anxiety/depression
- Safety:
  - GCS ↓ 2 points or ↑ 4 points on NIHSS that was sustained ≥8 hours in 1st 24 hours
  - Serious AEs within 72 hours
  - Death within 3 months
- Treatment Failures:
  - Primary – Failure to reach upper limit of blood pressure goals in each group within 2 hours after randomization
  - Secondary – Blood pressure remaining above upper limit in each group for 2 consecutive hours during period 2-24 hours after randomization

Baseline Characteristics

Mostly:
Age – early 60s
Slightly more males
Asian
GCS ≥12
SBP around 200 in ED
NIHSS 11 (0-40)
ICH size 10 cc in BG or thalamus
¼ had IVH

Table 1. Demographic and Clinical Characteristics of the Participants, According to Treatment Group.*

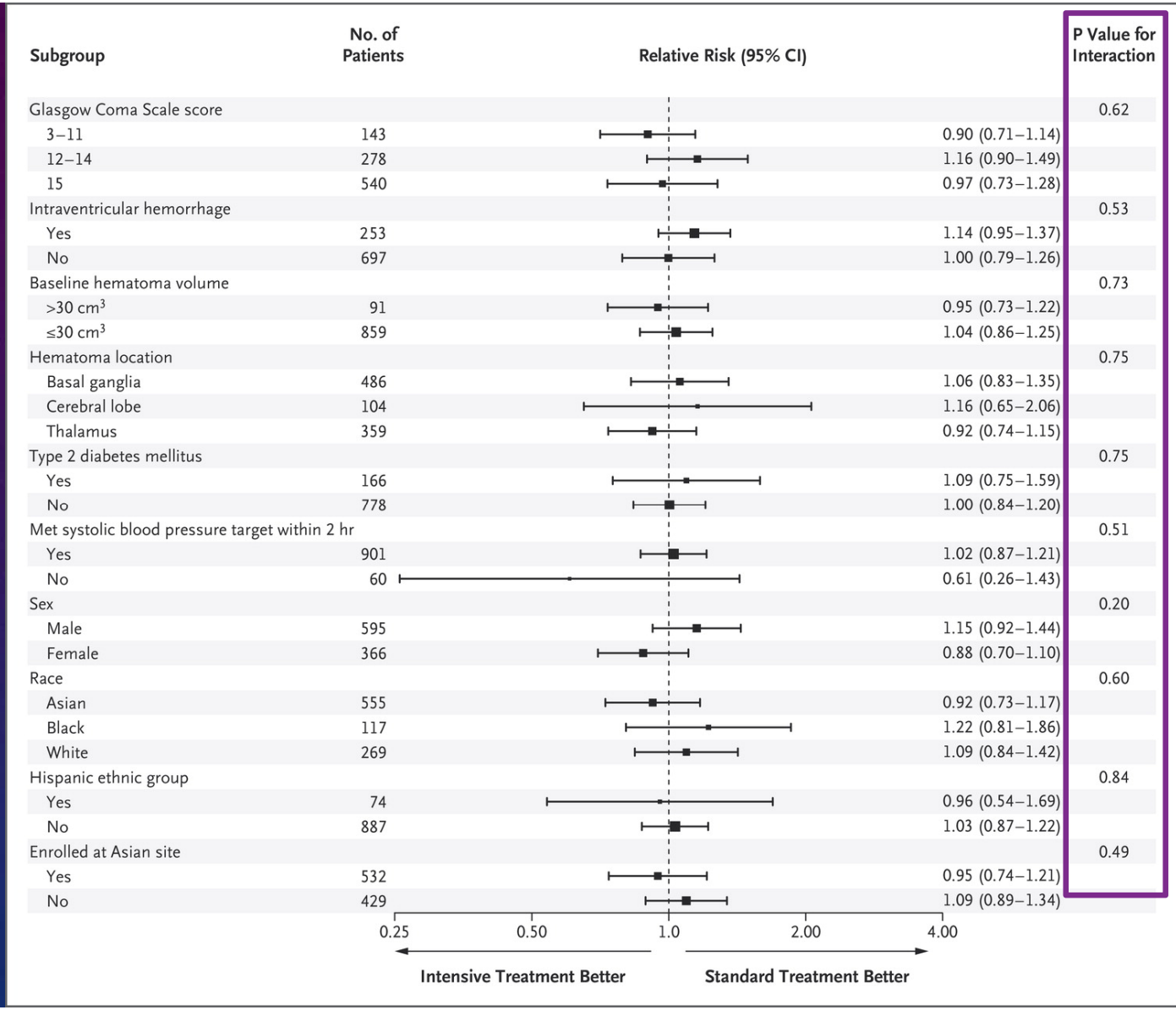
Characteristic	Intensive Treatment (N=500)	Standard Treatment (N=500)
Age — yr	62±13.1	61.9±13.1
Male sex — no. (%)	304 (60.8)	316 (63.2)
Race — no. (%)†		
Asian	277 (55.4)	285 (57.0)
Black	73 (14.6)	58 (11.6)
White	142 (28.4)	145 (29.0)
Other or unknown	8 (1.6)	12 (2.4)
Hispanic ethnic group — no. (%)†	38 (7.6)	41 (8.2)
Recruited at site in Asia — no. (%)	264 (52.8)	273 (54.6)
Glasgow Coma Scale score — no. (%)‡		
3–11	73 (14.6)	74 (14.8)
12–14	152 (30.4)	142 (28.4)
15	275 (55.0)	284 (56.8)
Systolic blood pressure at presentation in emergency department — mm Hg§	200±27.1	201.1±26.9
Median NIHSS score (range)¶	11 (0–40)	11 (0–40)
Intracerebral hematoma volume		
>30 cm^3 — no./total no. (%)	45/496 (9.1)	51/492 (10.4)
Median (range) — cm^3‖	10.3 (2.3–85.2)	10.2 (0.98–79.1)
Intraventricular hemorrhage — no./total no. (%)	122/496 (24.6)	142/492 (28.9)
Location of hemorrhage — no./total no. (%)		
Thalamus	193/496 (38.9)	180/492 (36.6)
Basal ganglia	255/496 (51.4)	251/492 (51.0)
Cerebral lobe	48/496 (9.7)	60/492 (12.2)
Cerebellum	0/496	1/492 (0.2)


Minimum Systolic Blood Pressure (mm Hg)
160
150
140
130
120
0
0
5
10
15
20
25
Hours since Randomization
Standard treatment
Intensive treatment

Results

Table 2. Primary, Secondary, and Safety Outcomes, According to Treatment Group.*

Outcome	Intensive Treatment (N=500)	Standard Treatment (N=500)	Unadjusted Analysis		Adjusted Analysis†	
			Relative Risk or Beta Estimate (95% CI)	P Value	Relative Risk or Beta Estimate (95% CI)	P Value
Primary outcome: death or disability — no./total no. (%)‡	186/481 (38.7)	181/480 (37.7)	1.02 (0.83 to 1.25)	0.84	1.04 (0.85 to 1.27)	0.72
Hematoma expansion — no./total no. (%)§	85/450 (18.9)	104/426 (24.4)	0.78 (0.59 to 1.04)	0.09	0.78 (0.58 to 1.03)	0.08
Neurologic deterioration within 24 hr — no. (%)¶	55 (11.0)	40 (8.0)	1.38 (0.92 to 2.07)	0.13	1.39 (0.92 to 2.09)	0.11
Treatment-related serious adverse event within 72 hr — no. (%)‖	8 (1.6)	6 (1.2)	1.33 (0.46 to 3.84)	0.59	1.37 (0.47 to 3.95)	0.56
Any serious adverse event within 3 mo — no. (%)	128 (25.6)	100 (20.0)	1.28 (0.99 to 1.66)	0.06	1.30 (1.00 to 1.69)	0.05
Hypotension within 72 hr — no. (%)	6 (1.2)	3 (0.6)	2.00 (0.50 to 8.00)	0.33	1.96 (0.49 to 7.87)	0.34
Death — no. (%)	33 (6.6)	34 (6.8)	0.97 (0.60 to 1.57)	0.90	0.99 (0.61 to 1.60)	0.97
EQ-5D utility index score**††			−0.01 (−0.05 to 0.02)	0.47	−0.02 (−0.05 to 0.02)	0.29
Median	0.7	0.7				
Range	−0.1 to 1.0	0 to 1.0				
EQ-5D visual-analogue scale score**‡‡			−1.14 (−5.28 to 2.99)	0.59	−1.32 (−5.25 to 2.60)	0.51
Median	62.5	70				
Range	0 to 100	0 to 100				


Subgroup
No. of Patients
Relative Risk (95% CI)
P Value for Interaction
Glasgow Coma Scale score 0.62
3–11 143 0.90 (0.71–1.14)
12–14 278 1.16 (0.90–1.49)
15 540 0.97 (0.73–1.28)
Intraventricular hemorrhage 0.53
Yes 253 1.14 (0.95–1.37)
No 697 1.00 (0.79–1.26)
Baseline hematoma volume 0.73
>30 cm3 91 0.95 (0.73–1.22)
≤30 cm3 859 1.04 (0.86–1.25)
Hematoma location 0.75
Basal ganglia 486 1.06 (0.83–1.35)
Cerebral lobe 104 1.16 (0.65–2.06)
Thalamus 359 0.92 (0.74–1.15)
Type 2 diabetes mellitus 0.75
Yes 166 1.09 (0.75–1.59)
No 778 1.00 (0.84–1.20)
Met systolic blood pressure target within 2 hr 0.51
Yes 901 1.02 (0.87–1.21)
No 60 0.61 (0.26–1.43)
Sex 0.20
Male 595 1.15 (0.92–1.44)
Female 366 0.88 (0.70–1.10)
Race 0.60
Asian 555 0.92 (0.73–1.17)
Black 117 1.22 (0.81–1.86)
White 269 1.09 (0.84–1.42)
Hispanic ethnic group 0.84
Yes 74 0.96 (0.54–1.69)
No 887 1.03 (0.87–1.22)
Enrolled at Asian site 0.49
Yes 532 0.95 (0.74–1.21)
No 429 1.09 (0.89–1.34)
0.25
0.50
1.0
2.00
4.00
Intensive Treatment Better
Standard Treatment Better

Conclusion

- **Renal adverse events: 9% intensive vs 4% standard therapy (p=0.002)**

- Treatment Failures:
  - **Primary – 12.2% intensive vs 0.8% standard (p<0.001)**
  - **Secondary – 15.6% intensive vs 1.4% standard (p<0.001)**

- **Overall though: NO difference in primary or secondary outcomes for standard vs intensive.** ∴ Can keep goal SBP of 140-179 for first 24 hours

- Trial discontinued for futility before could reach target enrollment of 1280 patients (for 90% power needed 1042 patients).

- Note: This is different than the recent ACC/AHA change to HTN cut-off to 130/80

Case 2

A 65 year-old lifelong non-smoker female with well-controlled diabetes and coronary artery disease with no prior stent or bypass who occasionally drinks alcohol is admitted to the inpatient floor for 3 days of cough, fatigue, and mild dyspnea. She is afebrile, normocardic, normotensive, normopneic, and with room air saturation of 92%. A chest x-ray shows a left lower lobe infiltrate without associated effusion. Her Pneumonia Severity Index is Class III (chronic anemia with hematocrit <30% and azotemia of 32). She has not recently been hospitalized and lives at home with her husband. She was started on levofloxacin in the emergency department so you continue this (she is allergic to macrolides and tetracyclines). After 3 days, she is much improved with respect to cough and breathing. You feel she can be safely discharged home with antibiotics. You remember seeing the recent IDSA guidelines on duration of therapy for community-acquired pneumonia but wonder if there is any data behind it. Should you prescribe for the standard 7-10 days or just 5 days total?

Research

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Duration of Antibiotic Treatment in Community-Acquired Pneumonia

A Multicenter Randomized Clinical Trial

Ane Uranga, MD; Pedro P. España, MD; Amaia Bilbao, MSc, PhD; Jose María Quintana, MD, PhD; Ignacio Arriaga, MD; Maider Intxausti, MD; Jose Luis Lobo, MD, PhD; Laura Tomás, MD; Jesus Camino, MD; Juan Nuñez, MD; Alberto Capelastegui, MD, PhD

TRIAL REGISTRATION clinicaltrialsregister.eu Identifier: 2011-001067-51

JAMA Intern Med. 2016;176(9):1257-1265. doi:10.1001/jamainternmed.2016.3633
Published online July 25, 2016.

Introduction

- In 2007, IDSA/ATS published guidelines on duration of antibiotic treatment for CAP
  - Minimum 5 days duration
  - Afebrile state for 48-72 hours
  - Maximum 1 CAP-associated instability criteria before discontinuing therapy
    - SBP <90, HR >100, RR >24, S_aO_2 <90%, P_aO_2 <60 mm Hg RA
  - BUT: based mainly on consensus and expert opinion.

- Need to validate IDSA/ATS guidelines

Study Design

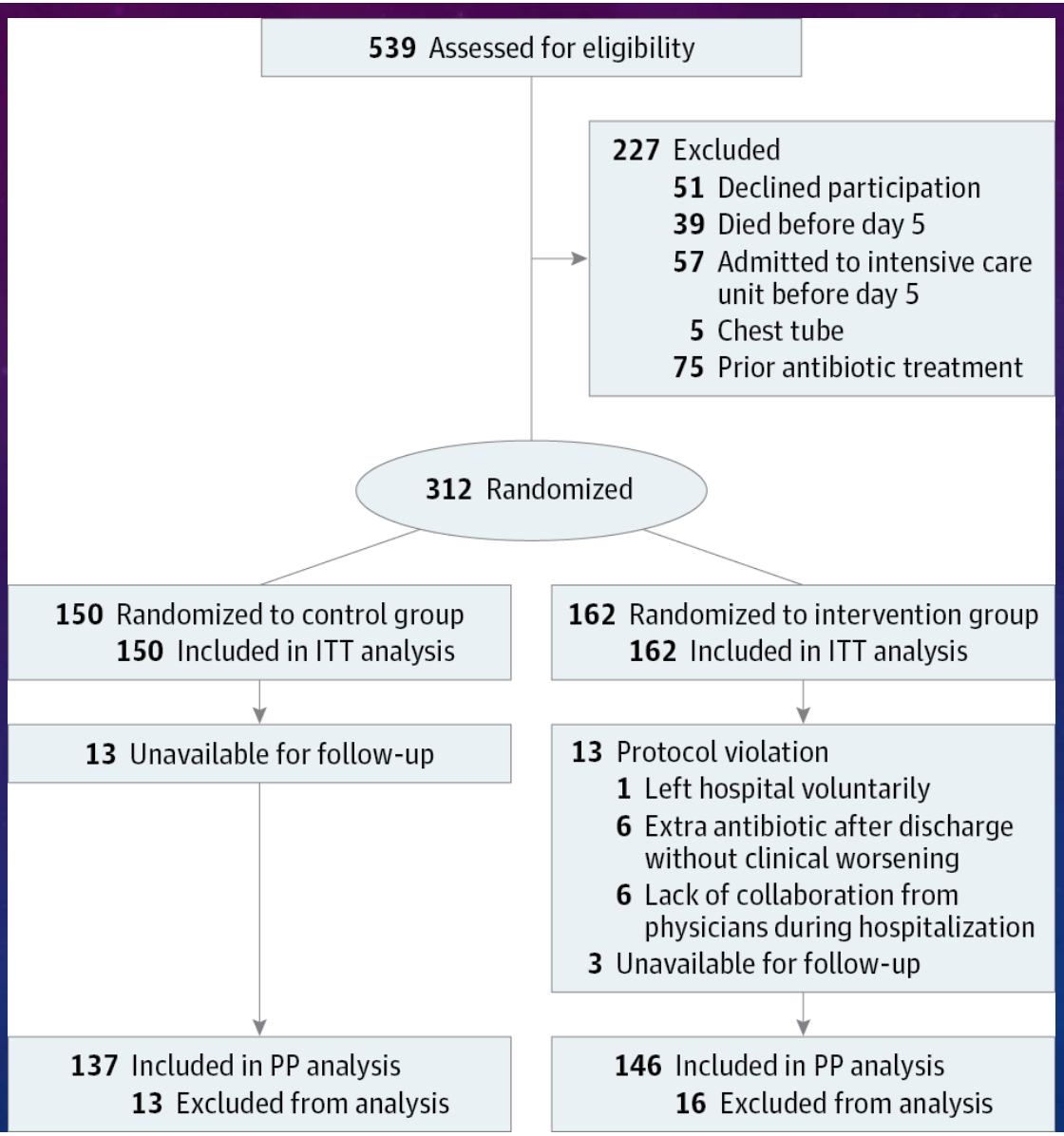
- Multi-center, non-inferior, randomized controlled trial & 30 day follow up (intention to treat & per protocol)
- 4 teaching hospitals in Spain Conducted 01 January 2012 to 31 August 2013 (1.6 years)

- Hospitalized patients, aged ≥18 with new infiltrate on CXR and 1 of: cough, fever, dyspnea, chest pain
- Exclude: HIV, organ transplant, splenectomy, prednisone >10 mg/d for >30d, other immunosuppressants, ANC <1000, nursing home resident, D/C from any healthcare setting within 14d, antibiotics in previous 30d, infection needing long duration of antibiotics, chest tube, extrapulmonary infection, ICU transfer

- 312 patients with CAP – randomized day 5 to intervention (stop antibiotics day 5 if temp <37.8^{o}C x 48h and max 1 sign of CAP-associated clinical instability) or to control (duration determined by local physician)

- Data collected:
  - Checked Pneumonia severity index within 4 hours of diagnosis
  - Co-morbitidies in Charlson Comorbidity Index
  - ADLs in Katz Index
  - Daily vitals to assess clinical stability

- If discharge <5 days, patient trained to check VS at home and then assessed in hospital on day 5
- Everyone evaluated in clinic on day 30


539 Assessed for eligibility
227 Excluded
51 Declined participation
39 Died before day 5
57 Admitted to intensive care unit before day 5
5 Chest tube
75 Prior antibiotic treatment
312 Randomized
150 Randomized to control group
150 Included in ITT analysis
162 Randomized to intervention group
162 Included in ITT analysis
13 Unavailable for follow-up
13 Protocol violation
1 Left hospital voluntarily
6 Extra antibiotic after discharge without clinical worsening
6 Lack of collaboration from physicians during hospitalization
3 Unavailable for follow-up
137 Included in PP analysis
13 Excluded from analysis
146 Included in PP analysis
16 Excluded from analysis

Outcomes

- Primary:
  - Clinical success (improvement/resolutions of signs/symptoms of pneumonia without further antibiotics) at days 10 and 30
  - CAP-related symptoms at days 5 and 10 (18-item CAP questionnaire – Chest 2002, 122(3): 920).

- Secondary at day 30:
  - Duration of antibiotic treatment
  - Time until clinical improvement
  - Time to return to normal activity
  - Radiographic resolution
  - In-hospital mortality
  - 30 day mortality
  - CAP recurrence
  - 30 day readmission
  - Hospital complications
  - Days with adverse events due to antibiotics
  - Length of stay in hospital

Mostly:
Age – mid 60s
2/3 males
Never or former smokers
Chronic metabolic syndrome diseases
Low co-morbidity
Very good functional/ADL status
Low to moderate pneumonia severity

Table 1. Baseline Characteristics of Study Participants[a]

Characteristic	Control Group (n = 150)	Intervention Group (n = 162)
Age, mean (SD), y	66.2 (17.9)	64.7 (18.7)
Sex		
Male	95 (63.3)	101 (62.3)
Female	55 (36.7)	61 (37.7)
Tobacco		
Current smoker	32 (21.3)	36 (22.6)
Never smoker	68 (45.3)	71 (44.7)
Former smoker	50 (33.3)	52 (32.7)
Alcohol consumption (yes)	24 (16.1)	17 (10.5)
Comorbidities		
Liver disease	4 (2.7)	4 (2.5)
Heart disease	38 (25.3)	39 (24.1)
Congestive heart failure	14 (9.3)	12 (7.4)
Cerebrovascular disease	16 (10.7)	9 (5.6)
Renal disease	12 (8.0)	12 (7.4)
COPD	21 (14)	27 (16.7)
Diabetes	25 (16.7)	21 (13.0)
Charlson Comorbidity Index, median (IQR)	1 (0-2)	1 (0-2)
Charlson Comorbidity Index, categorized		
0	61 (40.7)	70 (43.2)
1	37 (24.7)	47 (29.0)
>1	52 (34.7)	45 (27.8)
Katz Index, mean (SD)[b]	0.6 (1.6)	0.4 (1.3)
PSI class		
I-III	89 (59.3)	102 (63.0)
IV-V	61 (40.7)	60 (37.0)
PSI score, mean (SD)	83.7 (33.7)	81.8 (33.8)

Table 2. Results for the Primary Study Outcomes

Outcome	Control Group	Intervention Group	*P* Value
Intent-to-Treat Analysis			
Total No. of participants	150	162	
Clinical success, No. (%)[a]			
At day 10	71 (48.6)	90 (56.3)	.18
At day 30	132 (88.6)	147 (91.9)	.33
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.7 (11.4)	27.2 (12.5)	.10
At day 10	18.6 (9.0)	17.9 (7.6)	.69
Per-Protocol Analysis			
Total No. of participants	137	146	
Clinical success, No. (%)[a]			
At day 10	67 (50.4)	86 (59.7)	.12
At day 30	126 (92.7)	136 (94.4)	.54
CAP symptom questionnaire score, mean (SD)[b]			
At day 5	24.3 (11.4)	26.6 (12.1)	.16
At day 10	18.1 (8.5)	17.6 (7.4)	.81

Table 3. Clinical Success Rates at Days 10 and 30 Among Different Severity Groups Defined by PSI Class[a]

PSI Class	No. (%) of Participants		*P* Value
	Control Group	Intervention Group	
Clinical Success at Day 10			
PSI classes I-III			
Intent to treat	41/86 (47.7)	58/101 (57.4)	.18
Per protocol	39/80 (48.8)	58/94 (61.7)	.09
PSI classes IV-V			
Intent to treat	30/60 (50)	32/59 (54.2)	.64
Per protocol	28/53 (52.8)	28/50 (56)	.75
Clinical Success at Day 30			
PSI classes I-III			
Intent to treat	83/88 (94.3)	93/102 (91.2)	.41
Per protocol	80/82 (97.6)	89/95 (93.7)	.29
PSI classes IV-V			
Intent to treat	49/61 (80.3)	54/58 (93.1)	.04
Per protocol	46/54 (85.2)	47/49 (95.9)	.10

Table 4. Results for Secondary Study Outcomes in the Per-Protocol Analysis[a]

Outcome	Control Group (n = 137)	Intervention Group (n = 146)	*P* Value
Time, median (IQR), d			
Taking antibiotics	10 (10-11)	5 (5-6.5)	<.001
Not taking antibiotics	21 (10-27)	25 (5-32)	.001
Taking intravenous antibiotics	2 (1-4)	3 (2-4)	.22
Until clinical improvement	12 (8-18)	12 (7-15)	.41
Return to normal activity	18 (9-25)	15 (10-21)	.36
Radiographic resolution at day 30	93 (73.2)	112 (81.2)	.12
In-hospital mortality	2 (1.5)	3 (2.1)	>.99
30-d Mortality	3 (2.2)	3 (2.1)	>.99
Recurrence by day 30	6 (4.4)	4 (2.8)	.53
Readmission by day 30	9 (6.6)	2 (1.4)	.02
In-hospital complications			
Pleural effusion	10 (7.3)	5 (3.4)	.15
Treatment failure[b]	2 (1.5)	3 (2.1)	>.99
Respiratory failure[c]	26 (19.0)	31 (21.2)	.64
Severe sepsis[d]	7 (5.1)	8 (5.5)	.89
Renal failure[e]	5 (3.7)	6 (4.1)	.85
ICU admission	2 (1.5)	1 (0.7)	.61
Use of invasive mechanical ventilation	2 (1.5)	1 (0.7)	.61
Use of noninvasive mechanical ventilation	3 (2.2)	2 (1.4)	.67
Need for vasopressors	2 (1.5)	3 (2.1)	>.99
Antibiotic adverse effects by day 30	18 (13.1)	17 (11.7)	.72
Time with antibiotic adverse effects, mean (SD), d	3 (2.8)	1.7 (2.1)	.24
Length of hospital stay, mean (SD), d	5.5 (2.3)	5.7 (2.8)	.69

Conclusion

- 80% patients on quinolones, 10% on ß-lactam + macrolide
- Etiologic diagnosis found in 26.5% controls, 20.5% intervention (p=0.25)

- **5-day antibiotic course NOT inferior to longer duration but. . .**
  - **Based on clinical response and NOT set duration lengths**
  - **∴ May discontinue after 48 hours of clinical stability (70.1% of intervention group patients)**
- Choice of antibiotic did not matter – quinolone with or without ß-lactam or ß-lactam + macrolide
  - (also didn't matter 750 vs 500 mg levofloxacin)

- No difference in secondary outcomes except:
  - Duration of antibiotics
  - 30 day readmission rate – actually higher in control/longer duration group (p=0.02)

- Lack of difference even in severe cases (Pneumonia Severity Index 5) not in ICU.

- **SO: 5 days just as good for hospitalized CAP patients if afebrile and max 1 CAP-associated symptom**

Case 3

A 70 year-old nursing-home female resident presents to the emergency department with 2 days of productive cough, dyspnea, fever to 38°C, weakness, and loss of appetite. Her roommate recently had an upper respiratory infection. This patient has a history of hypertension, coronary artery disease, and diabetes. In the emergency department, her vitals are 38.3-115-26-93/47-88% RA. Her labs show these abnormalities: WBC 13K, pH 7.27, platelets 120K, bicarbonate 20. Creatinine was initially 1.1 and potassium 4.3. She is placed on 2 then 4 then 6 L/min supplemental oxygen but she remains tachypneic and tachycardic with evidence of fatigue. Because of impending respiratory failure, she is intubated in the emergency department and settled on an FiO_2 of 0.6. Her chest x-ray shows good placement of the endotracheal tube but also infiltrates in the RML, RLL, and LLL. GCS is now 8T. Because of recent history of Pseudomonas infection and likely healthcare-associated pneumonia, she is empirically started on vancomycin and an aminoglycoside. She is then admitted to ICU with diagnosis of HCAP with septic shock. Blood pressure drops to 75/45 despite IV fluids. She is started on norepinephrine at 2 and increased to 4 mcg/min for SBP>90. The next day, her creatinine increases to 1.8 and the day after to 3.1 for KDIGO AKI Stage 3. Her SAPS III score is now 79 (72% mortality) and SOFA is 12. Nephrology has been consulted. Her urine output has decreased to 150 mL/day but she is not severely hyperkalemic or azotemic. You wonder if dialysis should be started ASAP or delayed for as long as possible.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit

Stéphane Gaudry, M.D., David Hajage, M.D., Fréderique Schortgen, M.D., Laurent Martin-Lefevre, M.D., Bertrand Pons, M.D., Eric Boulet, M.D., Alexandre Boyer, M.D., Guillaume Chevrel, M.D., Nicolas Lerolle, M.D., Ph.D., Dorothée Carpentier, M.D., Nicolas de Prost, M.D., Ph.D., Alexandre Lautrette, M.D., Anne Bretagnol, M.D., Julien Mayaux, M.D., Saad Nseir, M.D., Ph.D., Bruno Megarbane, M.D., Ph.D., Marina Thirion, M.D., Jean-Marie Forel, M.D., Julien Maizel, M.D., Ph.D., Hodane Yonis, M.D., Philippe Markowicz, M.D., Guillaume Thiery, M.D., Florence Tubach, M.D., Ph.D., Jean-Damien Ricard, M.D., Ph.D., and Didier Dreyfuss, M.D., for the AKIKI Study Group*

Ministry of Health; ClinicalTrials.gov number, NCT01932190.)

Introduction

- For those critically ill in the ICU, there is no clear evidence on whether renal replacement therapy for acute kidney injury should be started early or late
- Pilot study in Kidney International in 2015 showed difference in mortality for early vs late RRT
- Review – KDIGO (Kidney Disease: Improving Global Outcomes) AKI Stages [Not used clinically]:
  - 1: Serum creatinine 1.5-1.9x baseline OR ≥0.3 mg/dL increase OR UOP <0.5 mL/kg/h x 6-12 hours
  - 2: Serum creatinine 2.0-2.9x baseline OR UOP <0.5 mL/kg/h ≥12 hours
  - 3: Serum creatinine >3x baseline OR ≥4.0 mg/dL increase OR start of RRT OR UOP ≤0.3 mL/kg/h x ≥24 hours OR anuria ≥12 hours

* UOP – urinary output

Study Design

- AKIKI trial – Artificial Kidney Initiation in Kidney Injury

- Multi-center, prospective, randomized controlled, open-label, unblinded
- 31 ICUs in France Conducted September 2013 to January 2016 (2.3 years) with 60 day follow-up

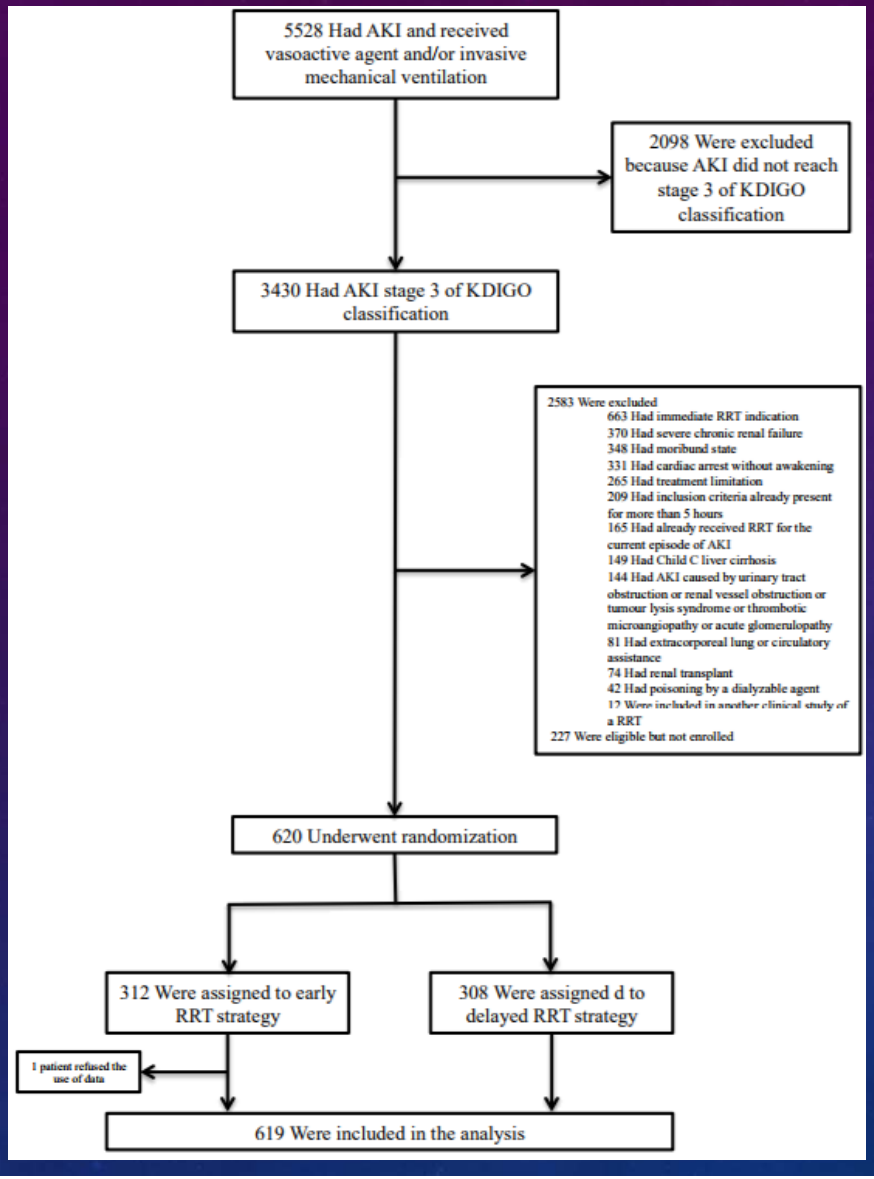
- Patients age >18 critically ill in ICU on mechanical ventilation, catecholamine infusion, or both with KDIGO Stage 3 with AKI due to ATN and no life-threatening complications due to AKI
- Early group: immediate dialysis (within 6 hours of diagnosis of KDIGO Stage 3)
- Delayed group: Dialysis started if K >6, pH <7.15, pulmonary edema (with either O_2 >5L for S_aO_2 >95% or F_iO_2 >50% on ventilator), BUN >112, OR oliguria >72 hours

- Type of dialysis at discretion of physician and site

- Stop dialysis: UOP >500 mL/24 h (earliest), strongly considered if UOP >1000 mL/24 h if off diuretics or >2000 mL /24 h if on diuretics, must stop if creatinine decreases on dialysis
- Restart dialysis: creatinine does not decrease further, UOP <1000 mL/24 h off diuretics or <2000 mL/24 h on diuretics

Exclusion Criteria

- Prior CKD
- AKI due to tract or vessel obstruction, TLS, thrombotic microangiopathy, or acute glomerulopathy
- Dialyzable poison
- Cirrhosis – Child class C
- Cardiac arrest without regaining consciousness
- Expected death in 24 hours
- Already received RRT for this AKI
- Extracorporeal cardiopulmonary therapy
- Renal transplant
- DNR



2583 Were excluded

663 Had immediate RRT indication

370 Had severe chronic renal failure

348 Had moribund state

331 Had cardiac arrest without awakening

265 Had treatment limitation

209 Had inclusion criteria already present for more than 5 hours

165 Had already received RRT for the current episode of AKI

149 Had Child C liver cirrhosis

144 Had AKI caused by urinary tract obstruction or renal vessel obstruction or tumour lysis syndrome or thrombotic microangiopathy or acute glomerulopathy

81 Had extracorporeal lung or circulatory assistance

74 Had renal transplant

42 Had poisoning by a dialyzable agent

12 Were included in another clinical study of a RRT

227 Were eligible but not enrolled

Outcomes

- Primary: mortality at day 60

- Secondary:
  - Dialysis ≥1 in delayed group
  - No. of days free from dialysis, dialysis catheter, mechanical ventilation, vasopressor use
  - SOFA score – days 3 and 7
  - Vitals – day 28
  - Length of stay in ICU and hospital
  - Proportion of patients DNR
  - No. of nosocomial infections
  - Complications directly due to AKI or RRT

Mostly:
Age – mid 60s
Normal creatinine without h/o CKD
Hypertensive
SAPS III of 70s
SOFA around 11
1 nephrotoxin, mostly aminoglycoside
Most – ventilated on vasopressors
Most – septic shock
Most – either oliguric or anuric
Developed:
- Creatinine in 3 range
- BUN in 50s
- Normal K
- Metabolic acidosis

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Early Strategy (N=311)	Delayed Strategy (N=308)
Age — yr	64.8±14.2	67.4±13.4
Serum creatinine before ICU admission — mg/dl†	0.95±0.26	0.97±0.31
Coexisting conditions — no. (%)		
Chronic renal failure	22 (7)	38 (12)
Hypertension	161 (52)	167 (54)
Diabetes mellitus	82 (26)	81 (26)
Congestive heart failure	24 (8)	32 (10)
Ischemic heart disease	30 (10)	32 (10)
SAPS III at enrollment‡	72.6±14.4	73.7±14.2
SOFA score at enrollment§	10.9±3.2	10.8±3.1
Exposure to at least one nephrotoxic agent in past 2 days — no./total no. (%)¶	194/311 (62)	195/308 (63)
Intravenous contrast	66/194 (34)	71/195 (36)
Aminoglycoside	106/194 (55)	106/195 (54)
Vancomycin	26/194 (13)	29/195 (15)
Physiological support — no. (%)		
Invasive mechanical ventilation	266 (86)	267 (87)
Vasopressor support with epinephrine or norepinephrine	265 (85)	263 (85)
Sepsis status — no. (%)‖		
Sepsis	25 (8)	21 (7)
Severe sepsis	16 (5)	19 (6)
Septic shock	209 (67)	204 (66)
Patients with oliguria or anuria — no. (%)	202 (65)	191 (62)
Serum creatinine — mg/dl	3.25±1.40	3.20±1.32
Blood urea nitrogen — mg/dl	53±24	54±24
Serum potassium — mmol/liter	4.4±0.7	4.4±0.7
Serum bicarbonate — mmol/liter	18.7±5.1	18.8±5.5

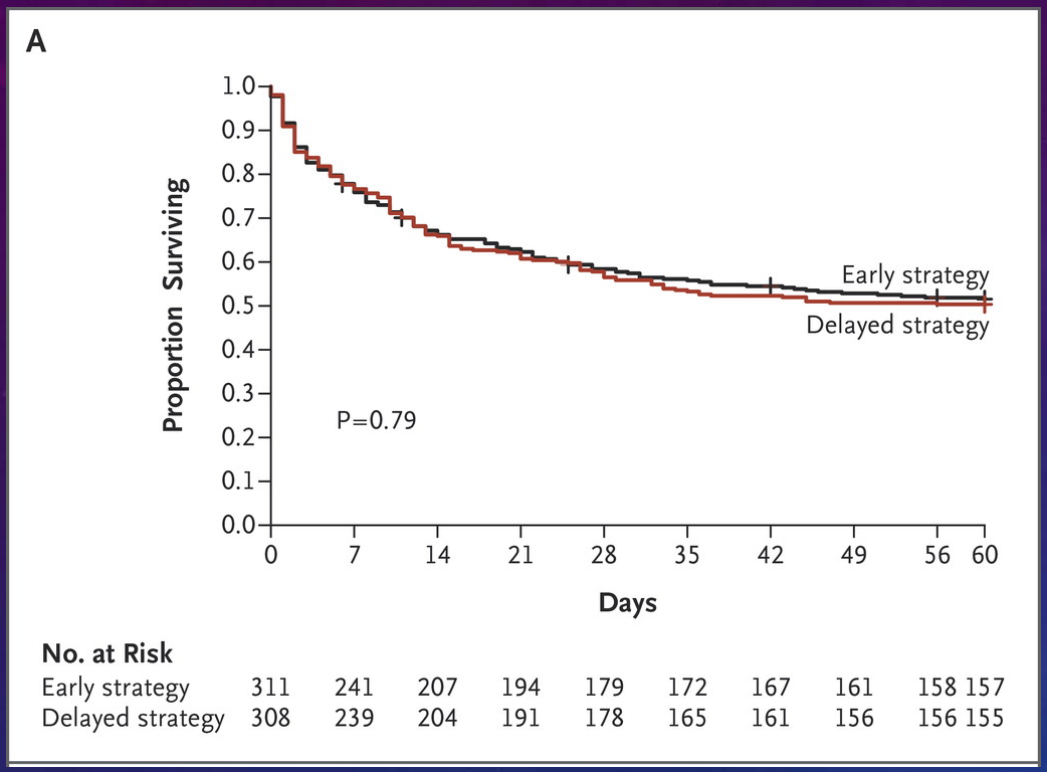
Table S4. Patient characteristics at the time of RRT initiation *

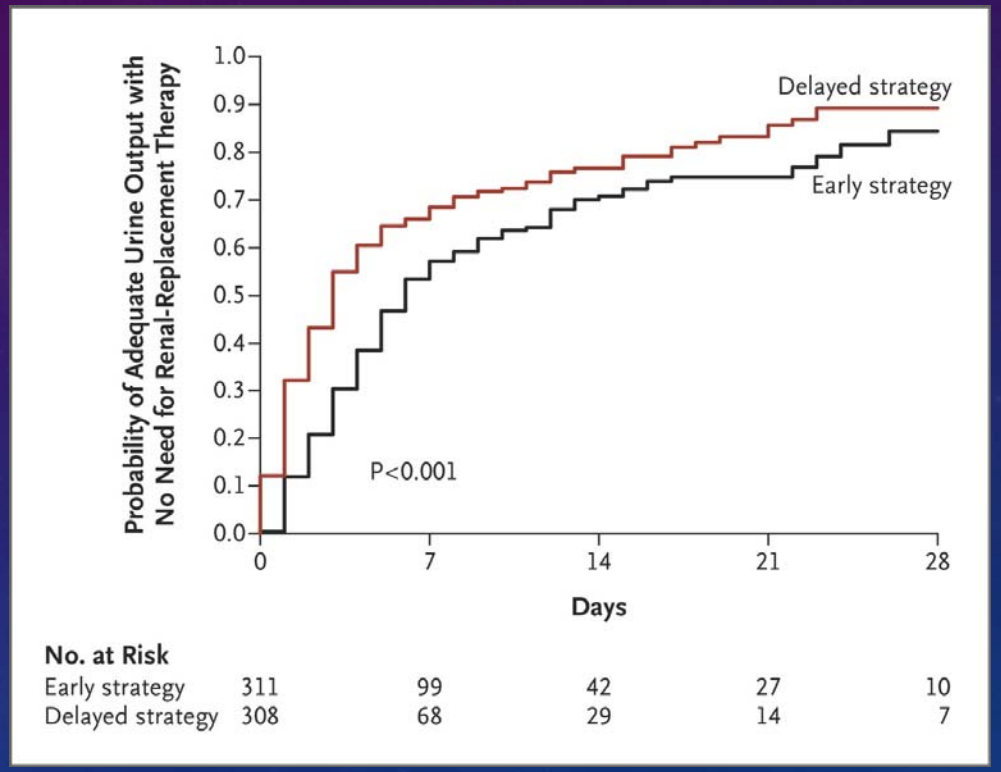
Characteristic	Early RRT strategy N=305 †	Delayed RRT strategy N=157	P Value
Urine output before RRT – ml/24h –median (IQR) ‡	—	150 (50-600)	
Serum creatinine – mg/dl	3.27±1.37	5.33±2.33	<0.001
Blood urea nitrogen – mg/dl	52±24	90±34	<0.001
Potassium – mmol/liter	4.4±0.7	5.1±0.9	<0.001
Bicarbonate – mmol/liter	18.9±4.9	16.6±5.6	<0.001
pH	7.30±0.12	7.25±0.15	<0.001
Sodium – mmol/liter	137.9±5.9	137.3±6.2	0.26
Invasive mechanical ventilation – no. (%)	264 (87)	138 (88)	0.75
Vasopressor (epinephrine or norepinephrine) support – no. (%)	254 (84)	125 (80)	0.30
Epinephrine dose – mg/hour	2.8±2.1	6.1±5.5	0.14
Norepinephrine dose – mg/ hour	4.2±4.2	5.6±7.5	0.57

Table 2. Primary and Secondary Outcomes and Adverse Events.*

Outcome	Early Strategy (N=311)	Delayed Strategy (N=308)	P Value	Hazard Ratio (95% CI)
Death — no. (% [95% CI])†				
Day 28	129 (41.6 [35.9–46.9])	134 (43.5 [37.7–48.8])		
Day 60	150 (48.5 [42.6–53.8])	153 (49.7 [43.8–55.0])	0.79	1.03 (0.82–1.29)
Adjusted analysis‡			0.84	1.02 (0.81–1.29)
Patients with treatment limitation in ICU — no. (%)§	71 (23)	73 (24)	0.78	
Median study day on which a treatment limitation first occurred (IQR)§	6 (2–12.5)	8 (3–14)	0.23	
Patients who received renal-replacement therapy — no. (%)	305 (98)	157 (51)	<0.001	
Median renal-replacement therapy–free days (IQR)	17 (2–26)	19 (5–29)	<0.001	
Median mechanical ventilation–free days (IQR)	7 (0–22)	6 (0–21)	0.76	
Median vasopressor-free days (IQR)	20 (1–26)	20 (0–26)	0.67	
SOFA score				
Day 3	10±4	10±4	0.14	
Day 7	8±4	8±4	0.63	
SOFA score without renal component				
Day 3	8±4	8±4	0.62	
Day 7	6±4	6±3	0.94	
Median length of ICU stay (IQR)				
Survivors	13 (8–23)	13 (7–23)	0.87	
Nonsurvivors	6 (2–14)	6 (2–13)	0.92	
Median length of hospital stay (IQR)				
Survivors	29 (17–51)	32 (20–51)	0.58	
Nonsurvivors	6 (2–14)	6 (2–13)	0.85	

Nosocomial infection			
Catheter-related bloodstream infection			
Patients with infection — no. (%)¶	31 (10)	16 (5)	0.03
Median incidence per 1000 catheter-days (IQR)	3.4 (2.3–4.6)	2.1 (1.1–3.1)	0.09
Unexplained bloodstream infection — no. (%)	21 (7)	26 (8)	0.43
Ventilator-associated pneumonia — no. (%)	50 (16)	37 (12)	0.15
Complications potentially related to acute kidney injury or renal-replacement therapy — no. (%)‖			
Hemorrhage	27 (9)	36 (12)	0.21
Thrombocytopenia	172 (55)	165 (54)	0.70
Thrombosis	11 (4)	16 (5)	0.31
Hypokalemia	69 (22)	67 (22)	0.95
Hypophosphatemia	69 (22)	46 (15)	0.03
Hyperkalemia	16 (5)	18 (6)	0.68
Cardiac rhythm disorders — no. (%)			
Severe	29 (9)	35 (11)	0.40
Moderate	49 (16)	48 (16)	0.77
Transfusion			
Patients who received transfusion — no. (%)	146 (47)	152 (49)	0.57
Units of red cells transfused per patient	2.4±4.1	2.4±4.3	0.75
Dependence on renal-replacement therapy — no./total no. (%)			
Day 28	22/179 (12)	17/178 (10)	0.51
Day 60	3/157 (2)	8/155 (5)	0.12


A
Proportion Surviving
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Early strategy
Delayed strategy
P=0.79
0 7 14 21 28 35 42 49 56 60
Days
No. at Risk
Early strategy 311 241 207 194 179 172 167 161 158 157
Delayed strategy 308 239 204 191 178 165 161 156 156 155


Probability of Adequate Urine Output with No Need for Renal-Replacement Therapy
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Delayed strategy
Early strategy
P<0.001
0 7 14 21 28
Days
No. at Risk
Early strategy 311 99 42 27 10
Delayed strategy 308 68 29 14 7

Conclusion

- Delayed strategy prevented 50% of dialyses in that group with no difference in mortality at day 60
- Recovery of renal function was more rapid in delayed group

- Limitation: Had only 1.2% mortality difference. Investigators expected 15% difference based on critical care literature 2010-2014. For power of 90%, would need 70K patients.

Case 4

A 50 year-old overweight (BMI 28 kg/m^2) woman comes in for her third bout of *Clostridium difficile* colitis in one year which started after a prolonged hospitalization for UTI with sepsis. She has no other gastrointestinal history, immunocompromising conditions, immunodeficiencies, or proton-pump inhibitor use. She has been on probiotic treatment, specifically *Saccharomyces boulardii* and has been treated with metronidazole and vancomycin. Her most recent treatment was a pulse-dose schedule of vancomycin in the last few days. You are concerned about the recurrences and wonder if a stool transplant (fecal microbiota transplantation) would be the most effective treatment for her with respect to cure and safety.

Annals of Internal Medicine

ORIGINAL RESEARCH

Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent *Clostridium difficile* Infection

A Randomized Trial

Colleen R. Kelly, MD; Alexander Khoruts, MD; Christopher Staley, PhD; Michael J. Sadowsky, PhD; Mortadha Abd, MD; Mustafa Alani, MD; Brianna Bakow, BA; Patrizia Curran, MD; Joyce McKenney, MS; Allison Tisch, NP; Steven E. Reinert, MS; Jason T. Machan, PhD; and Lawrence J. Brandt, MD

Primary Funding Source: National Institute of Diabetes and Digestive and Kidney Diseases.

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For author affiliations, see end of text.

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Introduction

- Until this trial, there were only limited data on the efficacy of fecal microbiota transplantation (FMT) in recurrent *C. diff* infections (CDI) in case series or open-label clinical trials

- *C. difficile* colitis - #1 healthcare-associated infection in U.S. 2011: 453K infections, 29K deaths
- Recurrence 15-35% after 1st episode, 65% after 2nd episode
- Colonoscopy delivery more common than NG – better efficacy, safety, patient acceptance/tolerance

- Objective: Determine efficacy and safety of FMT for recurrent CDI

- Plan:
  - FMT with donor (heterologous) stool or patient's own (autologous) stool by colonoscopy
  - Failed autologous FMT to get donor FMT
  - Failed donor FMT to get repeat donor FMT from different donor

Study Design

- Two-center, prospective, randomized, control trial, intention to treat
- Conducted 15 November 2012 to 10 March 2015 (2.3 years)
- Montefiore Medical Center, Bronx, NY *AND* Miriam Hospital, Providence, RI (Microbiome analysis @ UMN)

- 46 patients
  - age ≥18,
  - ≥3 CDI recurrences
    - (≥3 unformed stools/24 hours x 2 consecutive days AND +C diff test or pseudomembranes on colo)
  - failed after tapered or pulsed vancomycin or can't taper/DC vancomycin without recurrent diarrhea
  - completed at least 10 days vancomycin for most recent CDI
  - continued treatment 2-3 days prior to FMT

- Patients choose donor or use recruited healthy volunteer donors

- Testing:
  - Donors: HIV 2 weeks prior, 1 mo prior – Hepatitis A/B/C, *Treponema*, *C. diff* PCR, *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli*, *Listeria*, *Vibrio* spp., *Giardia*, *Cryptosporidia*, *Cyclospora*, *Isospora*, O&P, *Rotavirus*
  - Patients: HIV, Hepatitis A/B/C, *Treponema*

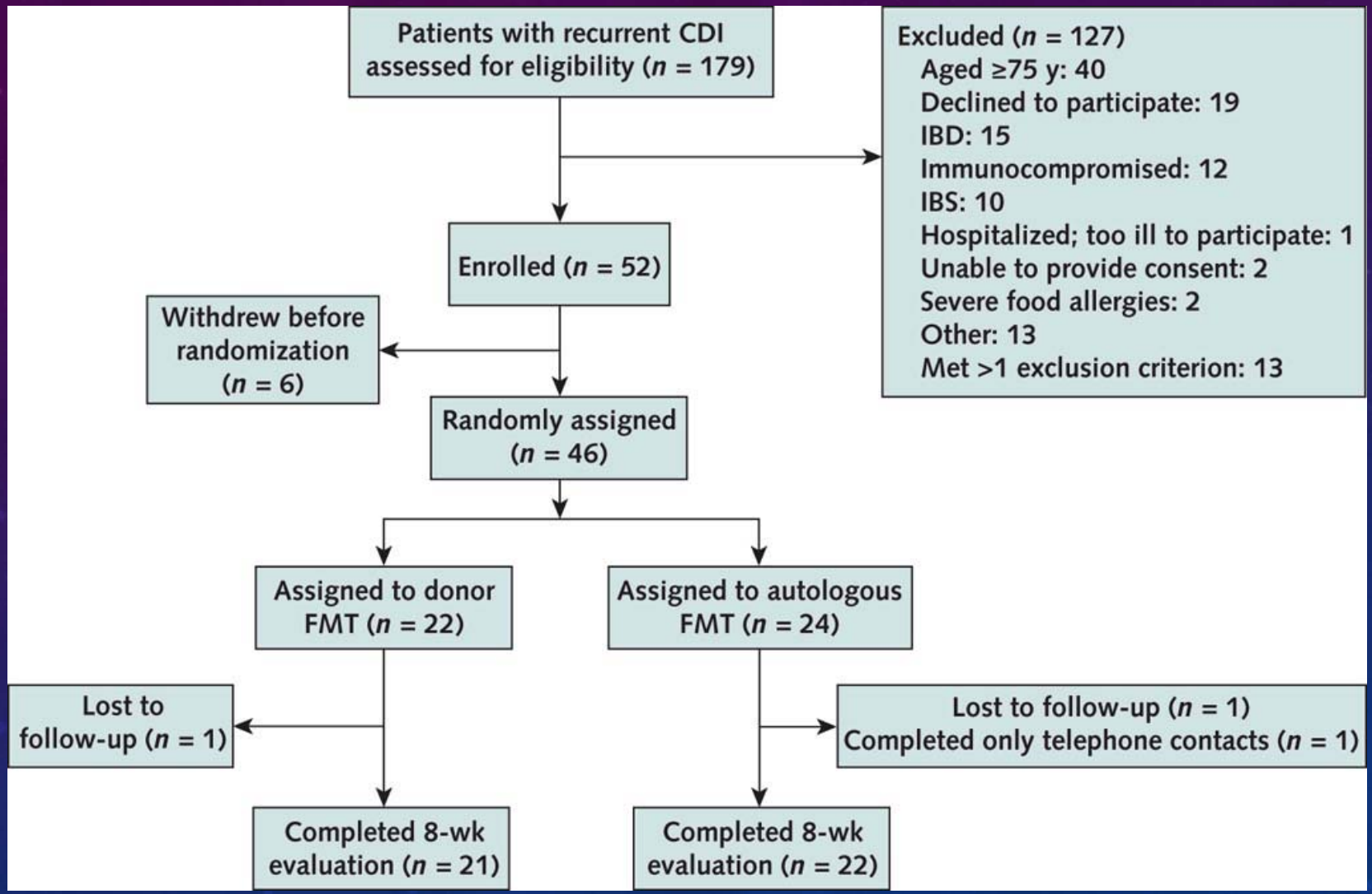
Exclusion Criteria

- Donors:
  - Known communicable disease
  - Metabolic syndrome
  - Diarrheal disorder
  - Autoimmune/atopic disorder
  - Tumor
  - Neurological disorder
  - Chronic pain syndrome
  - Antibiotic use for any reason in last 3 months

- Subjects/patients:
  - Age ≥75
  - IBD, IBS, chronic diarrheal disorder
  - Immunocompromised or immunodeficient
  - Anaphylactic food allergy
  - Previous FMT
  - Untreated colorectal cancer
  - Can’t get colonoscopy

Procedure

- Donors: $Mg(OH)_2$ the evening before with fresh stool collection next day, iced, processed <6 hours
- Patients: Bowel purge with Na_2SO_4, K_2SO_4, or $MgSO_4$ evening before then collect 1st stool for possible autologous FMT and keep iced/cool
- Patients equally allocated to donor and autologous FMT groups stratified by *C. diff* positivity
- Plan: 100 g stool in 500 mL NS immediately before procedure but not possible since frozen
  - Average 64 g stool used each procedure
- Administered 300 mL fecal suspension by colonoscopy to terminal ileum or cecum
- Patient retains for at least 1 hour
- Follow-up:
  - Patients contact team if diarrhea recurs. Also keep daily temperature
  - Diary of solicited AEs (fever, abdominal pain, bloat/gas, nausea/vomiting, diarrhea, constipation, anorexia) x 7 days, unsolicited x 30 days
  - Seen in clinic at 2 & 8 weeks where assessed for infectious and GI symptoms
  - Stool specimens at baseline and 2 & 8 weeks for *C. diff* testing and microbiome analyses
  - Contacted at 6 months for any serious AEs, new conditions, changes in existing conditions
- Microbiome analyses:
  - ≥5 days prior to FMT, then 2 and 8 weeks after


Patients with recurrent CDI assessed for eligibility (n = 179)
Excluded (n = 127)
Aged ≥75 y: 40
Declined to participate: 19
IBD: 15
Immunocompromised: 12
IBS: 10
Hospitalized; too ill to participate: 1
Unable to provide consent: 2
Severe food allergies: 2
Other: 13
Met >1 exclusion criterion: 13
Enrolled (n = 52)
Withdrew before randomization (n = 6)
Randomly assigned (n = 46)
Assigned to donor FMT (n = 22)
Assigned to autologous FMT (n = 24)
Lost to follow-up (n = 1)
Lost to follow-up (n = 1)
Completed only telephone contacts (n = 1)
Completed 8-wk evaluation (n = 21)
Completed 8-wk evaluation (n = 22)

Outcomes

- Primary:
  - Resolution of diarrhea without need for further anti-CDI treatment during 8-week follow-up or withdrawal (intention to treat)
  - Lack of recurrence with maintenance of resolution (<3 unformed stools/day) x 8 weeks without metronidazole, vancomycin, or fidaxomicin

- Secondary:
  - Adverse events including “serious”
  - New medical conditions for 6 months after FMT
  - Fecal microbiota analysis prior to and after FMT as well as on donor stool

Table 1. Baseline Characteristics of Enrolled Patients, by Group

Characteristic	Donor FMT (*n* = 22)	Autologous FMT (*n* = 24)
Mean age (SD), *y*	48 (16)	55 (14)
Female, *n (%)*	18 (82)	19 (79)
Mean body mass index (SD), *kg/m²*	28 (8)	27 (7)
Median Charlson Comorbidity Index score (range)	1 (0-4)	0 (0-3)
Mean duration of CDI since initial diagnosis (SD) [range], *mo*	9 (9) [3-36]	12 (12) [3-48]
Mean CDI recurrences (SD) [range], *n*	4 (2) [3-9]	5 (2) [2-10]
Mean duration of oral vancomycin therapy (SD) [range], *wk**	28 (36) [6-140]	23 (30) [8-148]
Prior probiotic treatment, *n (%)*	15 (68)	18 (75)
Prior *Lactobacillus* GG use, *n (%)*	5 (23)	3 (13)
Prior *Saccharomyces boulardii* use, *n (%)*	11 (50)	13 (54)
Prior rifaximin use, *n (%)*	3 (13)	1 (4)
Prior fidaxomicin use, *n (%)*	6 (27)	8 (33)
Proton-pump inhibitor use, *n (%)*	2 (9)	2 (8)

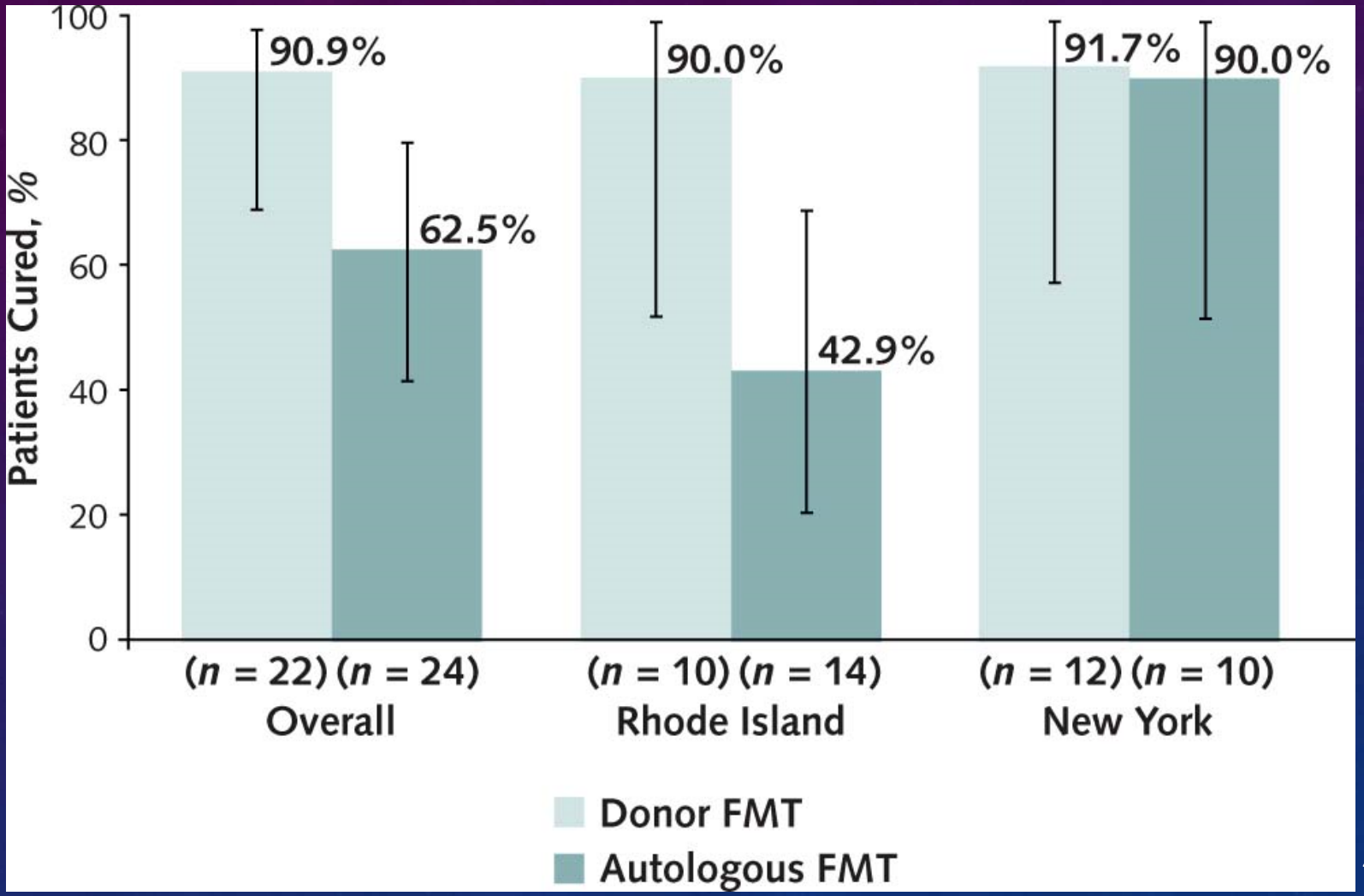
CDI = *Clostridium difficile* infection; FMT = fecal microbiota transplantation.
* For all prior CDI treatment courses combined; does not necessarily represent continuous use.

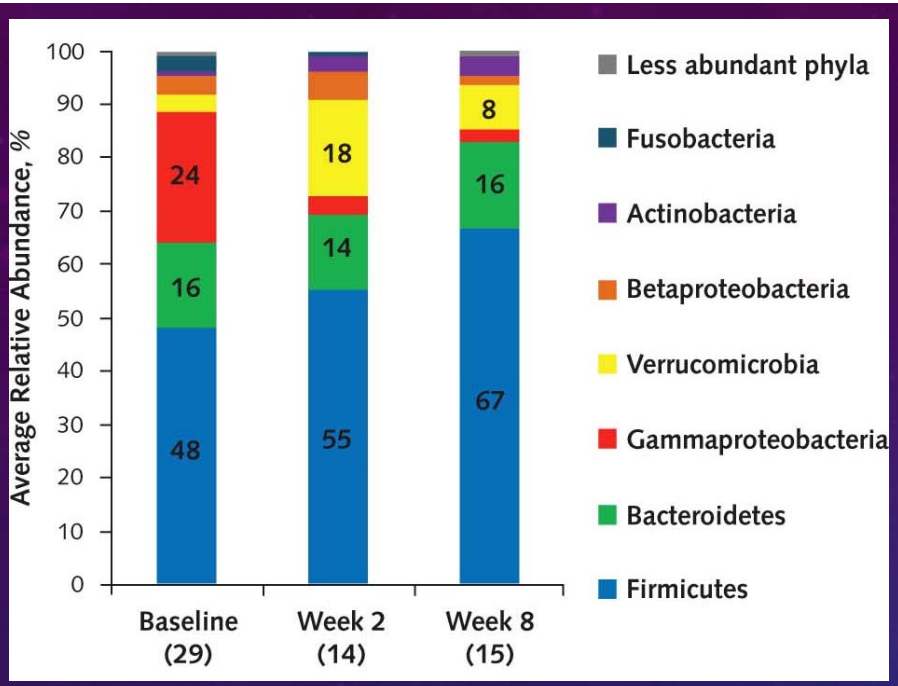
Mostly:

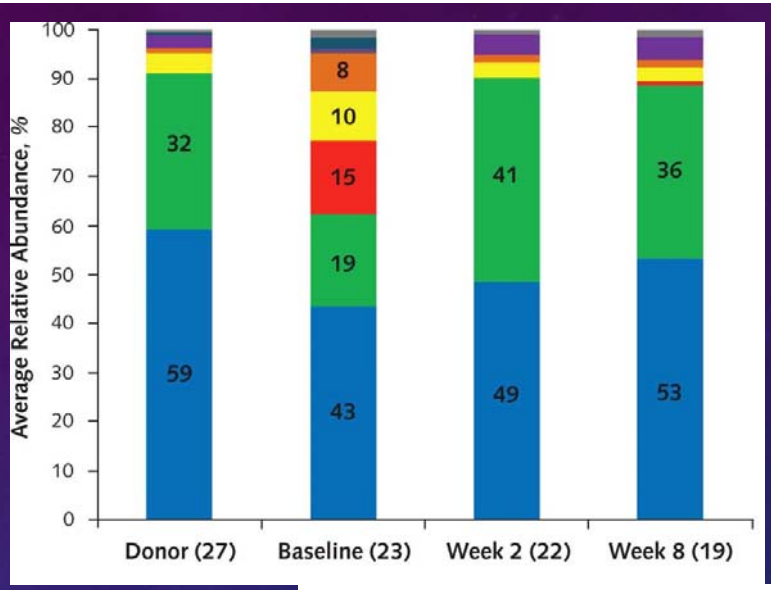
Age – 50s, female, overweight BMI, low co-morbidity

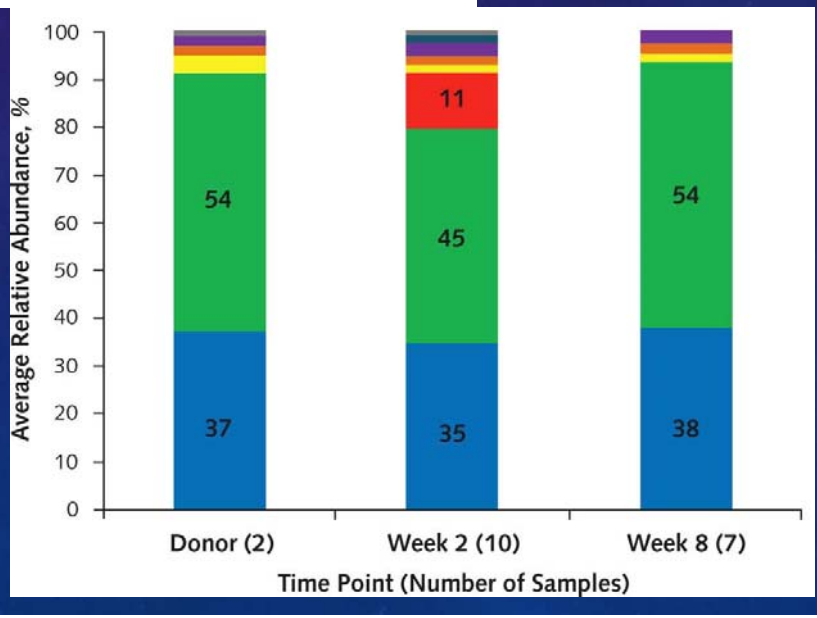
CDI duration (all recurrences) 9-12 months with average 4-5 recurrences

6 months oral vancomycin therapy + probiotics mostly *Saccharomyces boulardii*


Patients Cured, %
100
80
60
40
20
0
90.9%
62.5%
90.0%
42.9%
91.7%
90.0%
(n = 22) (n = 24)
Overall
(n = 10) (n = 14)
Rhode Island
(n = 12) (n = 10)
New York
Donor FMT
Autologous FMT







- Above: Autologous
- Upper Right: Donor
- Lower Right: Donor after relapse

Conclusion

- Average failure 10 days after FMT
  - 2 failures after donor FMT: one – 20 g stool, other – 60 g stool; one – cured after re-FMT different donor
  - 1 autologous failure lost to follow-up but PCP e-note later showed cure
  - 9 total autologous failures, all cured after donor FMT
  - ∴ cure rate single donor was 93.5%
- No difference between groups in AEs
- No serious AEs (4, 3 auto) or new/changed conditions (5) @ 6 mo due to FMT or colonoscopy

- **Therefore, donor FMT via colonoscopy is safe and more efficacious than autologous FMT**

- However, need further trials including elderly and immunocompromised patients
- Could not go beyond age 75 due to FDA regulation for investigational new drug application
  - But another study showed safety & efficacy of FMT in age >75
- Did not reach target of 48 patients (stopped at 46) because of data showing efficacy of FMT

Case 5

A 75 year-old woman was admitted from home through the emergency department for 5 days of worsening cough and dyspnea diagnosed as pneumonia with sepsis. She is normally independently ambulatory and able to perform all activities of daily living. This continued on the day of admission. She had history of coronary artery disease, hypertension, hyperlipidemia, controlled diabetes mellitus type 2 with mild nephropathy, CKD 3, cataracts, depression, GERD, osteoarthritis, past history of breast cancer, and diverticulosis. Because of the sepsis, she had a long protracted course in the hospital of 7 days but did not require intubation or vasopressors. During this time, however, she developed weakness such that she required assistance with transfers and for ambulation. She is improving but still quite weak. You wonder if there is a prognostic factor that can predict her clinical outcome once stable for discharge and if you should plan accordingly post-discharge besides possible durable medical equipment.

ORIGINAL RESEARCH

Prognostic Value of Braden Activity Subscale for Mobility Status in Hospitalized Older Adults

Vincenzo Valiani, MD[1,2*], Zhiguo Chen, PHHP-BIO[1-3], Gigi Lipori, MT, MBA[4], Marco Pahor, MD[1], Carlo Sabbá, MD[2], Todd M. Manini, PhD, FACSM[1*]

[1]Department of Aging & Geriatric Research, University of Florida, Gainesville, Florida; [2]Clinica Medica Cesare Frugoni, Dipartimento Interdisciplinare di Medicina, University of Bari Aldo Moro, Bari, Italy; [3]Department of Biostatistics, University of Florida, Gainesville, Florida; [4]UF Health, University of Florida, Gainesville, Florida.

Introduction

- The Braden or Morse scales are used to regularly rate physical functioning of patients
- Earlier study: Ability to rise from a chair – strong predictor of early discharge home

- Braden Scale for Predicting Pressure Sore Risk
  - 6 subscales: Sensory perception, Moisture, Activity, Mobility, Nutrition, Friction & Shear
  - Has high sensitivity in detecting changes in a patient's condition

- Can the Activity subscale predict post-hospital recovery and need for mobility interventions?

- Braden Activity Subscale (BAS): 1-4 (higher is better)
  - 1 – confined to bed
  - 2 – Severe limitation in walking, can't bear own weight, needs assistance to chair/wheelchair
  - 3 – Occasional walking but spends majority of day in bed
  - 4 – Walks outside room bid and inside room q2h while awake

- Objective: To evaluate the predictive value of the BAS for mobility impairment and recovery in the hospitalized elderly population

Study Design

- At University of Florida, Gainesville

- Single-center, retrospective, cohort
- Covered 01 January 2009 to 20 April 2014 (5.3 years)

- 19,769 patients aged ≥ 65
- Patients evaluated at admission (baseline) and every shift while in hospital

- Interrater reliability of BAS [published] = 0.96 At UF = 0.76 for day 1 for <3 d stay, 0.70 for ≥ 3 day
- Used DAILY average BAS: mobile ≥3, significant impairment <3

- Definitions:
  - Mobility impairment – ≥3 at admit then <3 during hospitalization
  - Incident mobility recover – the first instance BAS 4 reached
  - Mobility recovery event – <3 at admit but ≥3 during hospitalization

Outcomes

- Primary: discharge disposition and post-hospital mortality over 4.5 year follow up
  - Dispositions (9): Died in hospital, Other hospital admit [ACH, LTACH], Home, Home health, Hospice, Rehab, SNF, Healthcare facility [NH], Other [psychiatry, court, jail]

TABLE 1. Selected Baseline Characteristics of Study In-Hospital Patients

Characteristic	Overall Sample (N = 19,769)	Normal Mobility at Admission (n = 10,717)	Impaired Mobility at Admission (n = 9052)
Admission age, y	74.65 ± 7.46	73.73 ± 7.00	75.73 ± 7.84
Diagnosis count	13.09 ± 6.76	11.75 ± 6.17	14.67 ± 7.09
Median (IQR) length of stay	4 (2, 7)	3 (2, 6)	5 (3, 9)
Charlson Comorbidity Index	2.39 ± 2.33	2.22 ± 2.31	2.59 ± 2.34
Myocardial infarction	2032 (10.28%)	1037 (9.68%)	995 (10.99%)
Congestive heart failure	3545 (17.93%)	1674 (15.62%)	2871 (22.67%)
Peripheral vascular disease	2606 (13.18%)	1139 (10.63%)	1467 (16.21%)
Cerebrovascular disease	2800 (14.16%)	1021 (9.53%)	1779 (19.65%)
Dementia	706 (3.57%)	197 (1.84%)	509 (5.62%)
Diabetes	5225 (26.43%)	2679 (25.00%)	2546 (28.13%)
Cancer	3076 (15.56%)	1895 (17.68%)	1181 (13.05%)

NOTE: Except where indicated otherwise, values are n (%) for categorical variables and mean ± SD for continuous variables. All comparisons statistically different at $P < 0.001$. Abbreviation: IQR, interquartile range.

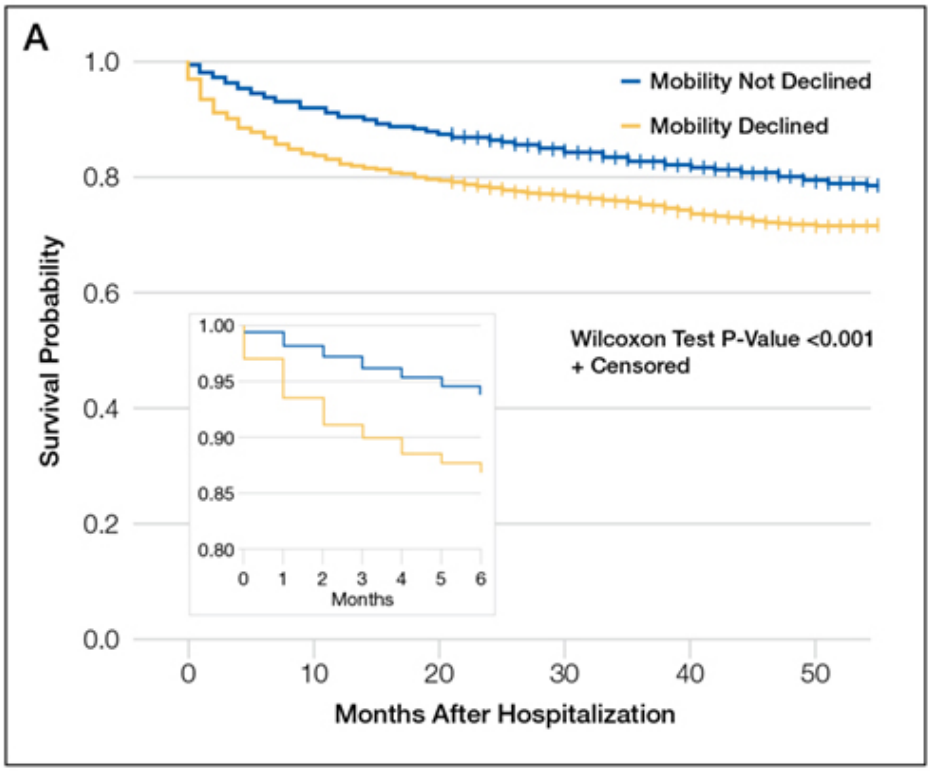
Mostly:
Age – mid 70s
LOS 4 days
12-14 diagnoses

TABLE 2. Odds Ratios, Confidence Intervals, and Restricted Mean Survival Time

Mobility	OR (95% CI) for Total Follow-Up Time	Survival Time for Total Follow-Up Time[a]	OR (95% CI) for ≤6 Months	Survival Time for ≤6 Months[a]	OR (95% CI) for >6 Months	Survival Time for >6 Months[a]
Decline	1.23[b] (1.08, 1.39)	39.7 (38.9, 40.4)	1.67[b] (1.40, 1.96)	2.1 (1.9, 2.3)	1.01 (0.86, 1.29)	45.4 (44.9, 45.9)
Recovery	0.54[b] (0.49, 0.59)	42.2 (41.7, 42.7)	0.38[b] (0.34, 0.43)	2.4 (2.2, 2.5)	0.84[b] (0.73, 0.96)	46.0 (45.7, 46.3)

- 10,717 observed walking frequently at admission
- 20.7% developed mobility impairment

- 9,052 had impairment at admission
- 52.3% recovered to walking occasionally or frequently



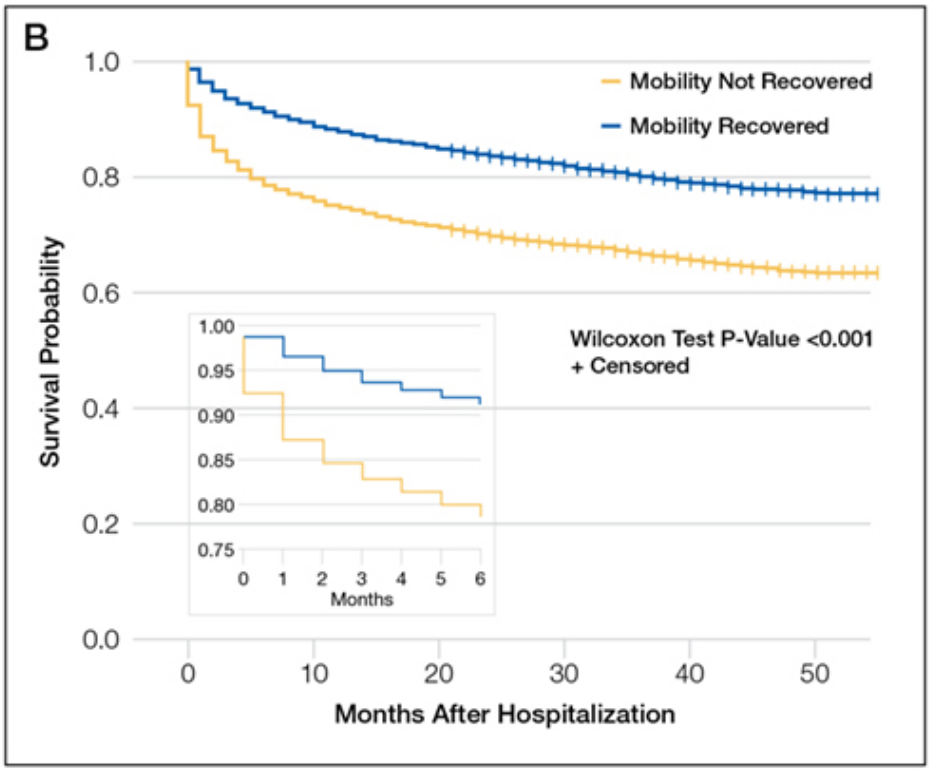


FIG. 1. Kaplan-Meier plot of survival probability (A) between patients with and without incident mobility impairment during hospitalization and (B) between patients with and without incident mobility recovery during hospitalization.

- If develop impairment in hospital, 1.23 x mortality – mostly over 1st 6 months
- If recover, OR mortality is 0.54 x ↓ than those who didn't – mostly over 1st 6 months
- Association between impairment and mortality gone >6 months after discharge

Conclusion

- Mobility impairment:
  - Sign of significant and rapid health decline
  - Need to intervene early
  - Those who recover in hospital have substantial mortality risk reduction
    - More likely to be discharged home or home health vs death or hospice
- **Therefore, BAS assessments of mobility status during hospitalization of elderly patients shows substantial prognostic value and could be used to target post-hospital care**
- Limitations: single center, no data on pre-hospital mobility status

Summary

- In acute cerebral hemorrhage, rapid correction of blood pressure to SBP 110-139 does not improve mortality, morbidity, or perceived quality of life over conservative correction to 140-179. Additionally, the aggressive approach does increase the rate of renal adverse effects.
- In hospitalized adults with community-acquired pneumonia and mild symptoms, 5 days of antibiotics or stopping upon 48 hours of clinical stability is sufficient treatment.
- In ICU adult patients on a ventilator and/or pressor support who have Stage 3 AKI, delaying dialysis for as long as possible rather than starting early did not affect mortality in-hospital and up to 60 days post-discharge.
- In recurrent C. difficile infections, donor fecal microbiota transplantation by colonoscopy was more effective than autologous transplant in achieving durable resolution.
- Mobility status by the Braden Activity Subscale can predict risk of mortality and need for specialized care post-discharge in hospitalized elderly patients.

Questions?

Thank You.

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Case 6

Same patient as Case 3. [A 70 year-old nursing-home female resident presents to the emergency department with 2 days of productive cough, dyspnea, fever to 38^{o}C, weakness, and loss of appetite. Her roommate recently had an upper respiratory infection. This patient has a history of hypertension, coronary artery disease, and diabetes. In the emergency department, her vitals are 38.3-115-26-93/47-88% RA. Her labs show these abnormalities: WBC 13K, pH 7.27, platelets 120K, bicarbonate 20. Creatinine was initially 1.1 and potassium 4.3. She is placed on 2 then 4 then 6 L/min supplemental oxygen but she remains tachypneic and tachycardic with evidence of fatigue. Because of impending respiratory failure, she is intubated in the emergency department and settled on an FiO_2 of 0.6. Her chest x-ray shows good placement of the endotracheal tube but also infiltrates in the RML, RLL, and LLL. GCS is now 8T. Because of recent history of Pseudomonas infection and likely healthcare-associated pneumonia, she is empirically started on vancomycin and an aminoglycoside. She is then admitted to ICU with diagnosis of HCAP with septic shock with SBP 74.] *SAPS II score is 48. You note that some of the ICU patients seem to be hyperoxygenated to S_pO_2 of 97% or higher. You wonder, as the advocate for your patient, if there is evidence that this strategy could improve your patient's outcome or cause harm.*

JAMA | Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit

The Oxygen-ICU Randomized Clinical Trial

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TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT01319643

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Introduction

- Many critically ill patients are kept hyperoxemic despite research showing harm

- Hyperoxemia can cause:
  - Lung toxicity (interstitial fibrosis, atelectasis, tracheobronchitis)
  - Systemic effects (peripheral vasoconstriction, increased production or reactive oxygen species)

- PROX1 trial (JAMA 2009): high F_iO_2 increases long-term mortality
- AVOID (Circulation 2015): STEMI without hypoxia – O_2 supplementation causes:
  - Early myocardial injury
  - Increased size of myocardial infarction at 6 months
- Yet, many patients still are overoxygenated

- Objective: Would a conservative approach to oxygenation result in improved outcomes for ICU patients?
  - Caveat for this study: "Conservative" means P_aO_2 70-100 mm Hg or S_aO_2 94-98%

Study Design

- Oxygen-ICU trial

- Single-center, prospective, randomized, open-label, modified intention to treat in a med-surg ICU in Italy
- Conducted 01 March 2010 to 30 October 2012 (2.6 years)

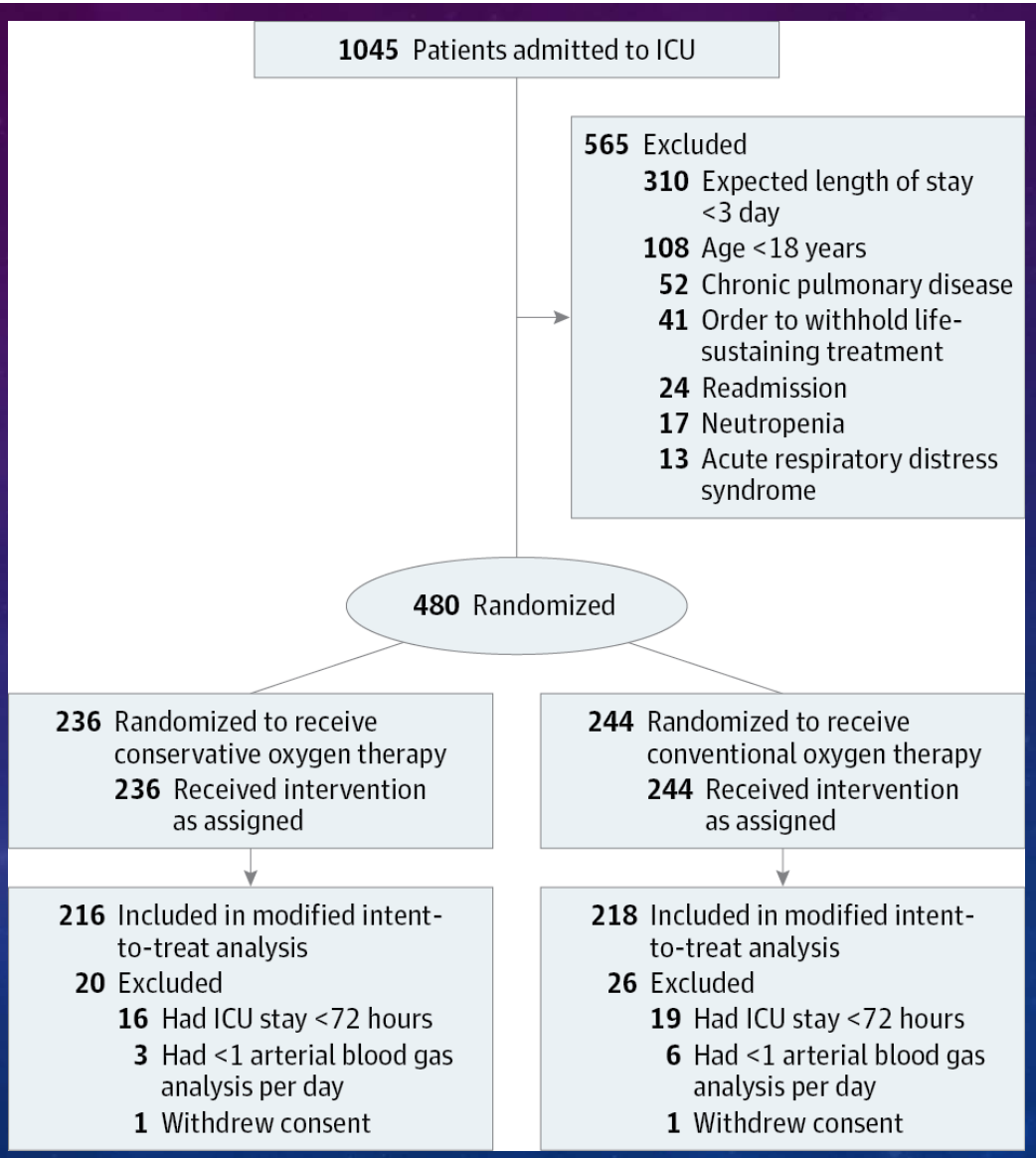
- Patients age >18 critically ill in ICU expected to last ≥72 hours
- Initially, 660 patients but stopped early due to enrollment issues after 480 patients *
  - Total: 434 patients – 216 conservative and 218 control

- Conservative group: Keep P_aO_2 at 70-100 mm Hg or S_aO_2 at 94-98% at lowest F_iO_2 to achieve this
- Control group: Keep P_aO_2 up to 150 mm Hg or S_aO_2 at 97-100% with minimum F_iO_2 of 0.4
- (this hospital's protocol - F_iO_2 of 1.0 for intubations, airway suction, hospital transfers)
- Use established criteria for decisions on NIV, intubation/extubation, ventilator settings
- Minimum 1 ABG/day and both F_iO_2 and P_aO_2 recorded daily
- Utilized SAPS II and SOFA scores

- Exclusions: age <18, pregnant, ICU readmission, DNR, immunosuppression or neutropenia, COPD exacerbation, ARDS with P_aO_2/F_iO_2 <150 (these last two exclusions due to different O_2 protocols)

- Only 480 patients, because in May 2012, city had 5.9 earthquake damaging the hospital with 23% decrease in hospital beds until end of 2013.
- Inclusion rate dramatically dropped. Needed 18-24 more months.
- Concerned of nursing bias after previous study period so trial stopped 10/30/12.

- 480 patients randomized
  - 236 conservative, 244 control
  - 216 conservative, 218 control (Mod ItT)



Outcomes

- Primary: ICU mortality

- Secondary:
  - New organ failure (respiratory, cardiovascular, hepatic, renal)
  - Infections ≥48 hours after ICU admit (hematologic, respiratory, surgical)
  - Re-operations in surgical patients
  - Hospital mortality
  - Ventilator-free hours

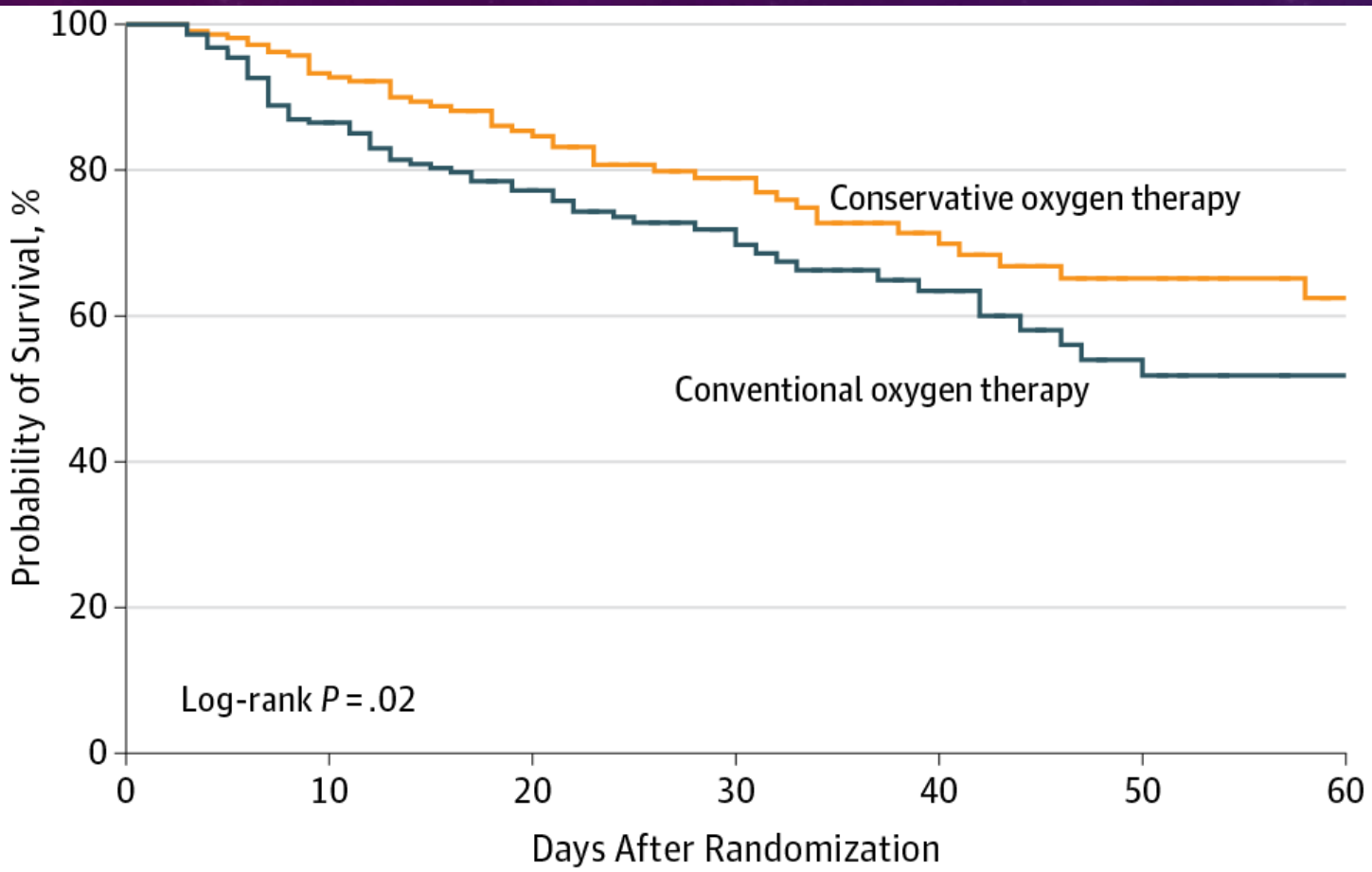
Mostly:
Age – mid 60s
Surgical patients
1/3 had cancer
Respiratory failure on ventilator
1/3 had shock of which 20% were septic
SAPS II of high 30s

Table 1. Characteristics of the Patients at Study Inclusion by Oxygen Therapy Group

	Oxygen Therapy Group, No. (%)	
	Conservative (n = 216)	Conventional (n = 218)
Sex, female	95 (44.0)	93 (42.7)
Age, median (IQR), y	63 (51-74)	65 (52-76)
Type of ICU admission		
Medical	77 (35.7)	86 (39.5)
Surgical	139 (64.3)	132 (60.7)
Preexisting condition		
Chronic obstructive pulmonary disease	7 (3.2)	11 (5.0)
Chronic renal failure	13 (6.0)	13 (6.0)
Chronic liver disease	28 (12.9)	31 (14.2)
Cancer	72 (33.3)	70 (31.1)
Respiratory failure	121 (56.0)	129 (59.2)
Mechanical ventilation	143 (66.2)	148 (67.9)
Shock	68 (31.4)	72 (33.0)
Septic	46 (21.3)	47 (21.6)
Hypovolemic or hemorrhagic	7 (3.2)	9 (4.1)
Cardiogenic	12 (5.6)	8 (3.7)
Mixed	3 (1.4)	8 (3.7)
Liver failure	40 (18.5)	45 (20.6)
Renal failure	32 (14.8)	35 (16.1)
Documented infections[a]	81 (37.5)	88 (40.4)
SAPS II, median (IQR) score[a]	37 (26-49)	39 (28-55)

Table 2. Primary and Secondary Outcomes

	Oxygen Therapy, No. (%)			
	Conservative (n = 216)	Conventional (n = 218)	Absolute Risk Difference (95% CI)	*P* Value
Primary outcome				
ICU mortality	25 (11.6)	44 (20.2)	0.086 (0.017 to 0.150)	.01
Secondary outcomes				
Hospital mortality	52 (24.2)	74 (33.9)	0.099 (0.013 to 0.182)	.03
New organ failure during ICU stay	41 (19.0)	56 (25.7)	0.067 (−0.012 to 0.145)	.09
Respiratory failure	14 (6.5)	14 (6.4)	−0.126 (−0.189 to −0.064)	.98
Shock	8 (3.7)	23 (10.6)	0.068 (0.020 to 0.120)	.006
Liver failure	4 (1.9)	14 (6.4)	0.046 (0.008 to 0.088)	.02
Renal failure	26 (12.0)	21 (9.6)	−0.024 (−0.084 to 0.035)	.42
New infections during ICU stay	39 (18.1)	50 (22.9)	0.049 (−0.027 to 0.124)	.21
Respiratory	30 (13.9)	37 (17.0)	0.031 (−0.038 to 0.099)	.37
Bacteremia	11 (5.1)	22 (10.1)	0.050 (0.000 to 0.090)	.049
Surgical site[a]	10 (7.2)	12 (9.1)	0.019 (−0.048 to 0.088)	.68
Surgical revision[a]	18 (12.9)	16 (12.1)	−0.008 (−0.088 to 0.073)	.84
Mechanical ventilation–free hours, median (IQR)	72 (35 to 110)	48 (24 to 96)	24 (0 to 46)	.02
ICU length of stay, median (IQR), d	6 (4 to 10)	6 (4 to 11)	0 (0 to 2)	.33
Hospital length of stay, median (IQR), d	21 (13 to 38)	21 (12 to 34)	0 (−5 to 1)	.21



No. at risk							
Conservative oxygen therapy	216	201	188	181	173	170	169
Conventional oxygen therapy	218	189	172	163	158	152	152

Conclusion

- Absolute risk reduction with conservative approach – 8.6%
- U-shaped relationship between P_aO_2 and mortality
  - Highest mortality when P_aO_2 exceeded 107 mm Hg

- **Therefore, keeping P_aO_2 between 70-100 mm Hg results in better outcomes, including mortality, in ICU patients than higher P_aO_2 levels.**

- However, need larger, multi-center trial

MOC Question 1

A 75 year-old woman is admitted for sepsis due to an acute urinary tract infection. She develops hypotension requiring norepinephrine support. Then, she develops altered mental status and respiratory failure requiring intubation. A CT abdomen/pelvis with contrast shows no pyelonephritis or GI pathology. On day 2, she develops acute kidney injury stage 3 with creatinine 4.1 with a baseline of 1.5 and no prior renal history. Her potassium is now 5, pH 7.25 with elevated lactate, no pulmonary edema, BUN 75, and still making urine at 400 mL in an 8-hour shift. You consult nephrology for the AKI. She recommends dialysis as soon as possible. Do you agree with this plan or do you recommend waiting for now?

A) Dialysis now
B) Delay dialysis until creatinine >5
C) Delay dialysis until potassium = 5.8
D) Delay dialysis until BUN = 90
E) Delay dialysis until potassium = 6.1 or urinary output drops to 400 mL/24 h x 3 days

Answer

E) Delay dialysis until potassium = 6.1 or urinary output drops to 400 mL/24 h x 3 days

Answer Explanation

Delaying dialysis in AKI KDIGO Stage 3 including in ventilated ICU patients on vasopressors until K >6, pH <7.15, pulmonary edema is present with O_2 >5 L or F_iO_2 >50%, BUN >112, or oliguria >72 hours resulted in less chance of catheter-related bloodstream infections and fosters faster renal recovery without affecting mortality.

1. Gaudri, Stéphane *et al.* for the AKIKI Study Group. Initiation strategies for renal replacement therapy in the intensive care unit. NEJM 375 (2016): 122-133.
2. Wald, Ron *et al.* for the Canadian Critical Care Trials Group. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. Kidney International 88 (2015): 897-904.

MOC Question 2

A 60 year-old man presents with two days of cough and dyspnea due to community-acquired pneumonia. You start him on cephalosporin and macrolide antibiotics. On day 4, he is normotensive, tachycardic to 102, and saturating 95% on 1 L/min oxygen. You plan on discharging him today. When should you stop antibiotics?

A) Today
B) Tomorrow
C) Day after tomorrow (day 6)
D) After 3-6 more days (day 7-10)

Answer

C) Day after tomorrow (day 6)

Answer Explanation

According to the IDSA guidelines and a recent study, 5 days of antibiotics is sufficient but more importantly, antibiotics may be stopped after 48 hours of clinical stability (afebrile and maximum 1 CAP-associated symptom defined as hypotension, tachycardia, tachypnea, desaturation <90%, or P_aO_2 <60 mm Hg).

1. Uranga, Ane *et al.* Duration of antibiotic treatment in community-acquired pneumonia: A multicenter randomized clinical trial. JAMA Intern Med 176 (2016): 1257-1265.