Clinical Year Review 2016: Critical Care Medicine

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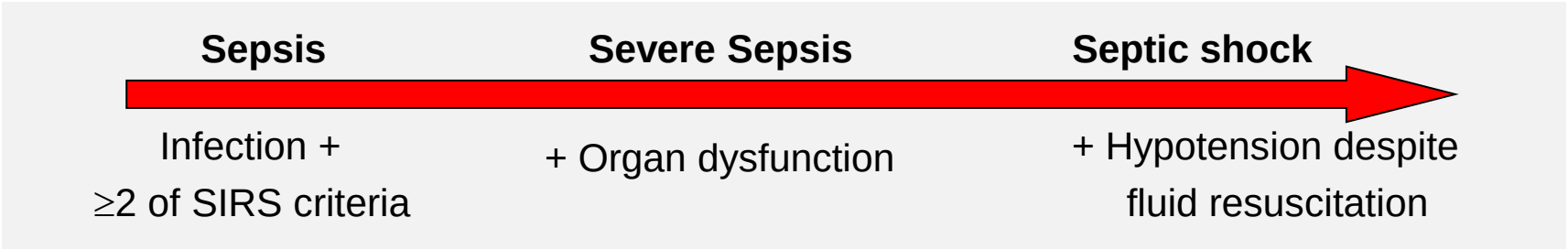
I.

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

A Need for New Definitions



Bone RC, et al. Chest 1992;101:1644-55

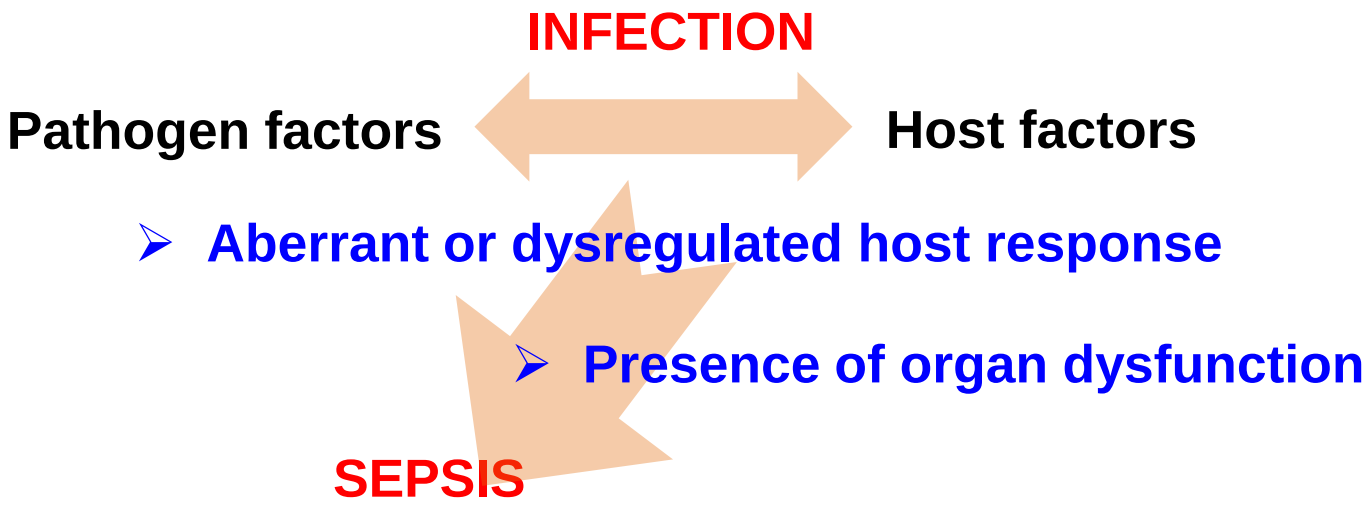
- **Public need**
  - Understandable definition of sepsis
- **Health care practitioners require**
  - Improved clinical prompts
  - Earlier identification
  - Accurate quantification of the burden

- **Task force (n=19)**
- **SCCM/ ESCIM** 2014'

- 31 International Professional Societies

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

Definitions of Sepsis



Preexisting acute illness, long-standing comorbidities, medication, and interventions

Modified Clinical And Biological Phenotype

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.

JAMA. 2016; 315(8):801-810. doi:10.1001/jama.2016.0287

Definitions of Organ Dysfunction

Acute change in total SOFA score ≥2 points consequent to the infection.

Sequential [Sepsis-Related] Organ Failure Assessment Score Vincent JL, et al. . Intensive Care Med. 1996;22(7):707-710.

System		Score				
		0	1	2	3	4
Respiration (PaO_2/FIO_2, mmHg)		≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation (Platelets, $\times 10^3/\mu L$)		≥150	<150	<100	<50	<20
Liver (Bilirubin, mg/dL)		<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular		MAP ≥70 mm Hg	MAP <70 mm Hg	DP <5 or DB (any dose)	DP 5.1-15 or Epi ≤0.1 or NE ≤0.1	DP >15 or Epi >0.1 or NE >0.1
CNS (Glasgow Coma Scale)		15	13-14	10-12	6-9	<6
Renal	**Cr (mg/dL)**	<1.2	1.2-1.9	2.0-3.4	3.5-4.9	>5.0
	UO, mL/d				<500	<200

- The baseline SOFA score: “0” in patients not known to have preexisting OD
- Presenting with modest dysfunction can deteriorate further
- Overall mortality risk SOFA score ≥2 with suspected infection ≒10%

JAMA. 2016; 315(8):801-810. doi:10.1001/jama.2016.0287

Bedside Surrogate For Organ Dysfunction By Quick SOFA (qSOFA)

Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly "**Identified at the bedside with qSOFA"**.

Bedside clinical score, qSOFA

At least 2 of following	▪ Respiratory rate ≥22/min ▪ Altered mentation ▪ Systolic blood pressure ≤100 mmHg

JAMA. 2016; 315(8):801-810. doi:10.1001/jama.2016.0287

Definitions of Septic Shock

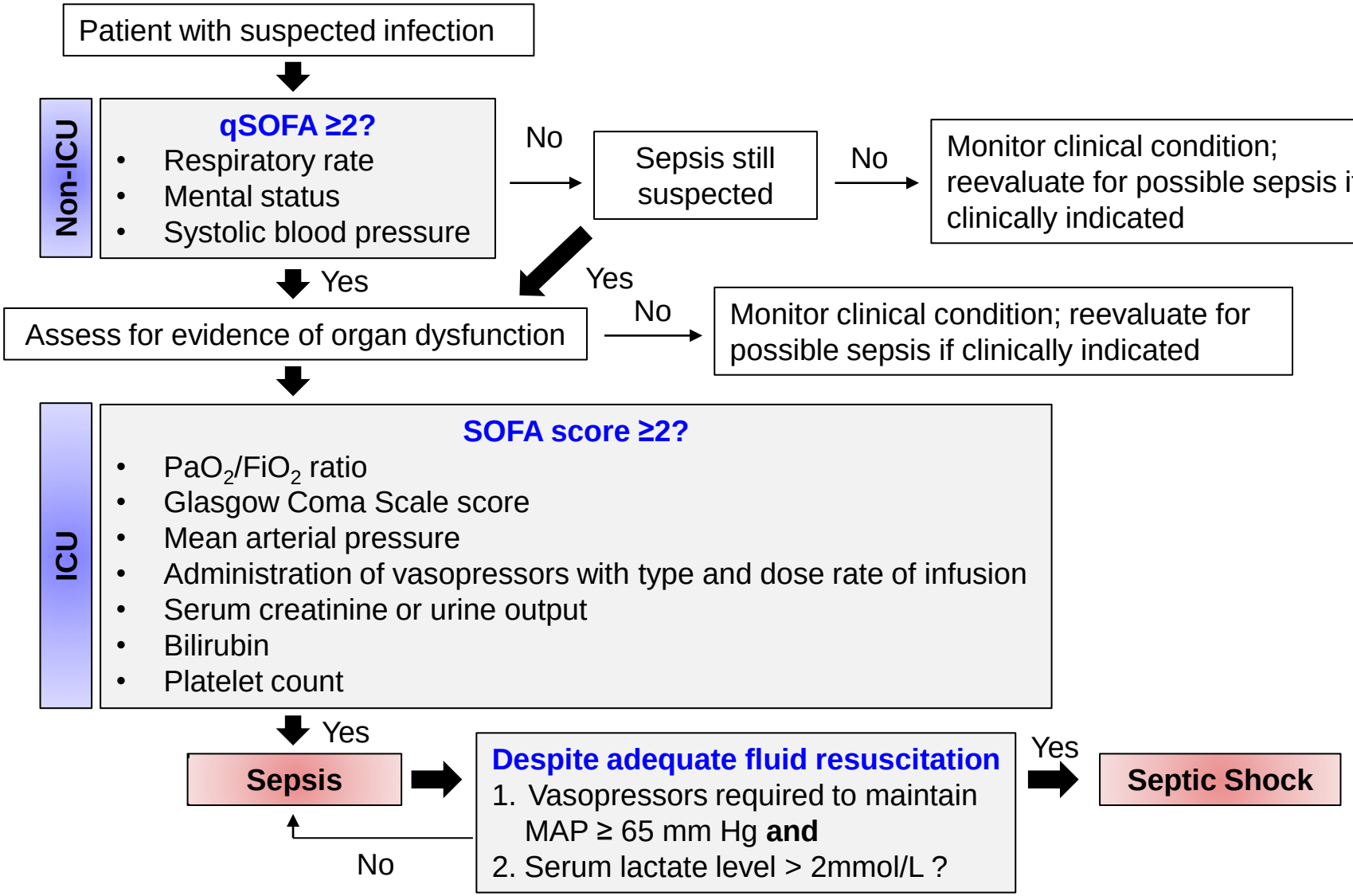
Subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality (>40%).

Clinical construct of sepsis with despite adequate volume resuscitation

- Persisting hypotension requiring vasopressors to maintain MAP ≥65 mmHg
- Serum lactate level >2 mmol/L (18mg/dL)

JAMA. 2016; 315(8):801-810. doi:10.1001/jama.2016.0287

Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



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SUMMARY

- Limitations of previous definitions
  - Excessive focus on inflammation, SIRS
  - Misleading model “sepsis -- severe sepsis – septic shock”
  - **Severe sepsis was redundant**

Earlier Recognition And More Timely Management

	Sepsis	Septic Shock
Sepsis-3 Definition	Life-threatening organ dysfunction caused by a dysregulated host response to infection	Subset of sepsis in which underlying circulatory and cellular/ metabolic abnormalities are profound enough to substantially increase mortality
Sepsis-3 Clinical criteria	Suspected or documented infection + acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis and vasopressor therapy needed to elevate MAP ≥65 mm Hg & lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

A Systematic Review And Meta-analysis of EGDT For Septic Shock: The ARISE, ProCESS and ProMISe Investigators

Objective

To determine whether **EGDT reduces mortality compared with other resuscitation strategies** for patients presenting to ED with adult or pediatric septic shock.

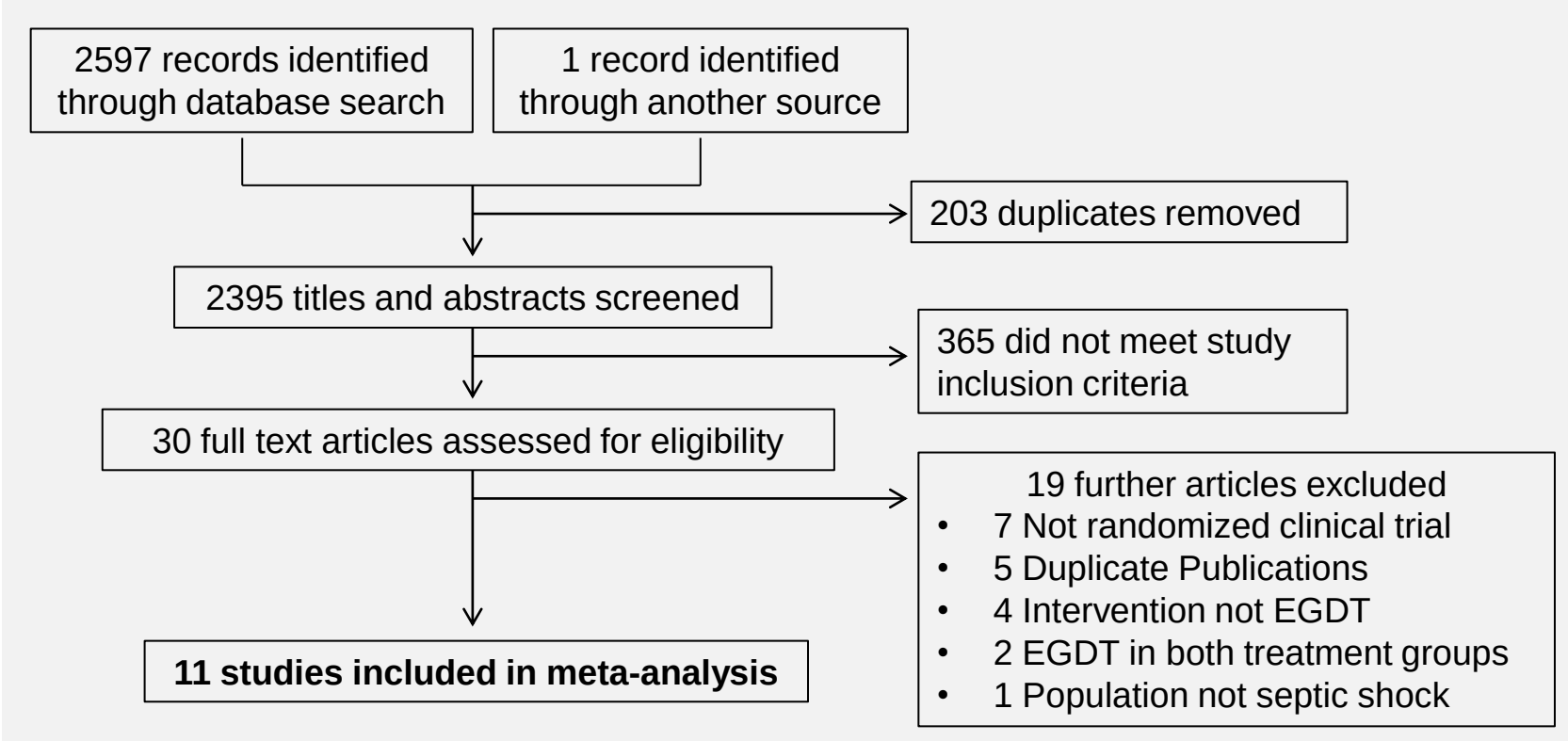
Methods

- RCTs, published from January 2000 to January 2015
- **Primary analysis**: pooled OR of mortality
- **Secondary outcomes**: organ support and hospital and ICU length of stay
- **Definition of EGDT**
  - Protocolized administration of IV fluids, vasoactive agents and RBC TF
  - Hemodynamic goals: CVP, MAP and $ScvO_2$

Intensive Care Med. 2015; 41:1549–1560 DOI 10.1007/s00134-015-3822-1

Results

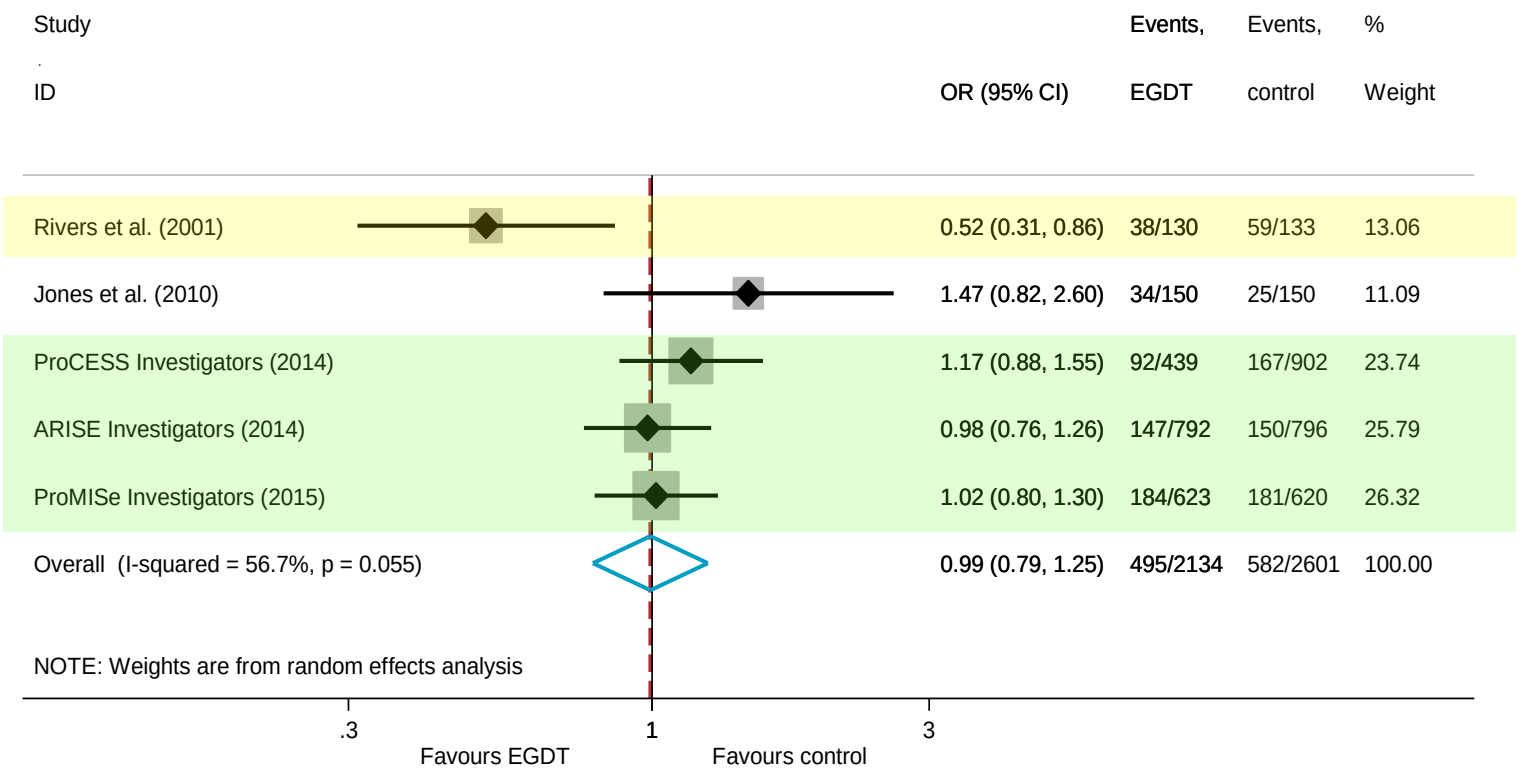
- N = 4,735 patients



Intensive Care Med. 2015; 41:1549–1560 DOI 10.1007/s00134-015-3822-1

Results

- Overall mortality: EGDT 23.2 % (495/2,134) vs. Control 22.4 % (582/2,601)



EGDT did not confer a reduction in overall mortality.

Intensive Care Med. 2015; 41:1549–1560 DOI 10.1007/s00134-015-3822-1

Results

	Relative effect (95 % CI)	Assumed event rate	EGDT event rate
28-day mortality	0.95 (0.82–1.10)	22.6 %	21.7%
90-day mortality	0.99 (0.80–1.15)	26.7 %	26.5%
In-hospital mortality	1.00 (0.87–1.16)	20.3 %	20.3%
ICU admission	**2.19 (1.82–2.65)**	**82.9 %**	**91.4%**
ICU length of stay	-0.02 (-0.47 to 0.43)	5–6 days	
Receipt of MV	0.97 (0.86 to 1.10)	34.9 %	34.2%
Duration of MV	0.48 (-0.34 to 1.30)	0.48 (-0.34 to 1.30)	
Receipt of vasopressors	**1.25 (1.10–1.40)**	**60.5 %**	**65.6%**
Duration of vasopressors	0.09 (-1.12 to 0.29)	2.4–2.5 days	
Receipt of RRT	0.99 (0.81–1.22)	10.1 %	10.1 %
Duration of RRT	-0.36 (-1.75 to 1.03)	5–9 days	

- **EGDT increased vasopressor use and ICU admission.**
- **No significant changes of duration of organ support and ICU length of stay.**

Intensive Care Med. 2015; 41:1549–1560 DOI 10.1007/s00134-015-3822-1

SUMMARY

- Meta-analysis of 11 published RCTs of EGDT does not show improved survival.
- EGDT is associated with increased vasopressor and ICU admission rate.
- No significant changes of duration of organ support and ICU length of stay.

Is “EGDT Protocol” Dead?

Intensive Care Med. 2015; 41:1549–1560 DOI 10.1007/s00134-015-3822-1

The Surviving Sepsis Campaign Bundles And Outcome: Results From The International Multicenter Prevalence Study On Sepsis (The IMPreSS study)

Objective

The aims of this study were to improve our understanding of how **compliance with the 3-h and 6-h SSC bundles** are used in different geographic areas, and how this relates to outcome.

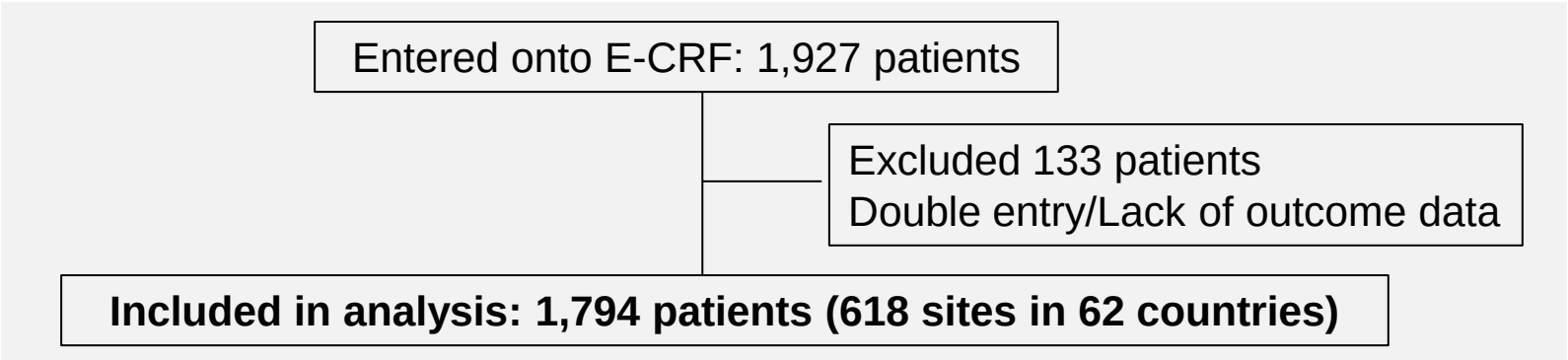
Methods

- Global, prospective, observational, quality improvement study
- Compliance with the SSC bundles in patients with either severe sepsis or septic shock
- On 7 November 2013 (0000 to 2400 hours), consecutive patients presenting to either the ED or ICU

- Suspicious of infection + SIRS + acute organ dysfunction and/or shock
- Followed up until 30 days after study enrolment or hospital discharge

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Results



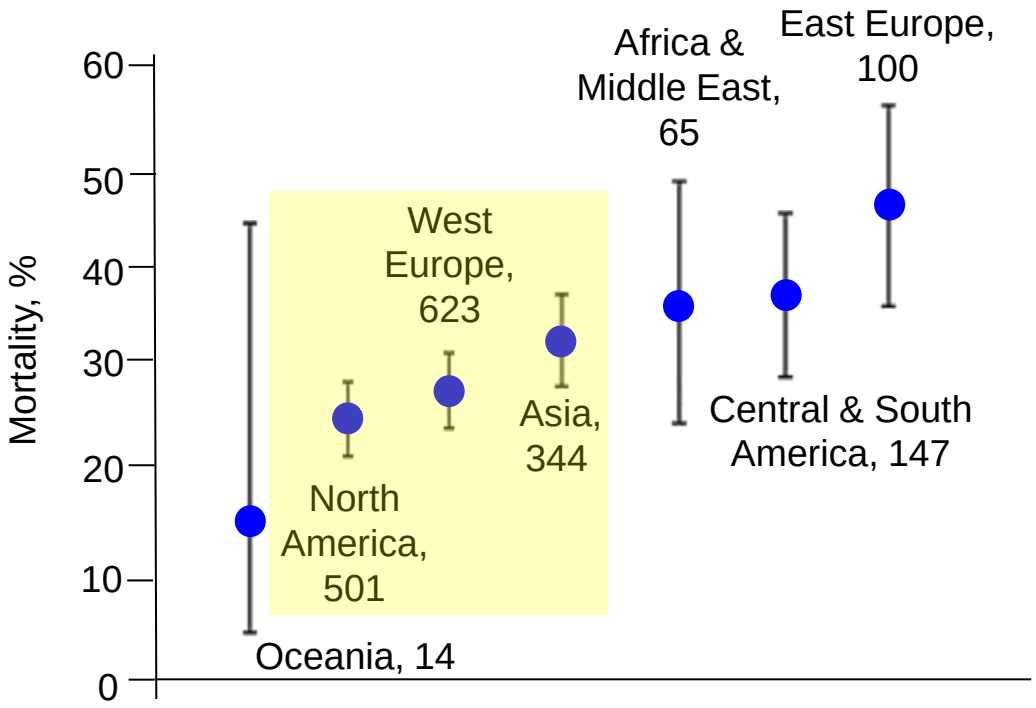
- Age > 65 years old (47 %)
- Western Europe (623, 34.7 %), North America (501, 27.9 %)

- **Presented with at least one co-morbid illness** (59 %)
  - Hypertension(48.4 %), diabetes (30.8 %), chronic lung disease (30 %)
- **Organ dysfunctions at presentation**
  - Hypotension (66 %), ARDS (57 %), AKI (46 %)

- Sepsis progressed to septic shock (39 %)
- ICU admission (86%)
- Median length of hospital stay 13.7 (6.5-24.6) days

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Results



Estimated mortality by region where the number represents the observations within each region.

- **Hospital mortality rate was 28.4 %.**
- **Significantly between different geographic regions**

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Results

Surviving Sepsis Campaign bundle compliance and associated hospital mortality			*<0.0001
3-h bundle compliance (all patients, n = 1,794)			
Measurement of lactate	1,002 (55.9)	BC before administration of AB	883 (49.2)
Broad-spectrum IV antibiotics	1,155 (64.4)	IV 30 mL/kg crystalloid for HPO	1,017 (56.7)
Full bundle		**340 (19.0)**	
H mortality for compliance	**67/340 (19.7)**	H mortality for noncompliance	**443/1,454 (30.5)***
6-h bundle compliance (all patients, n = 1,794)			
Repeat the lactate measurement	1,077 (60.0)	Measurement of CVP	1,209 (67.4)
Vasopressors for HPO	1,479 (82.4)	Measurement of $ScvO_2$	1,070 (59.6)
Full bundle		**637 (35.5)**	
H mortality for 6-h B compliance	**143/637 (22.4)**	H mortality for noncompliance	**367/1,157 (31.7)***
6-h bundle compliance for only patients with persistent hypotension MAP <65 mmHg & /or lactate >4 mmol/L after volume administration (n = 824)			
Repeat the lactate measurement	530 (64.3)	Measurement of CVP	274 (33.2)
Vasopressors for HPO	544 (66.0)	Measurement of $ScvO_2$	135 (16.4)
Full bundle		**90 (10.9)**	
H mortality for 6-h B compliance	**25/90 (27.8)**	H mortality for 6-h B noncompl.	**261/734 (35.6)**

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Results

Hospital mortality odds ratios based on general estimating equation population-averaged logistic regression models						
Detail	Unadjusted H mortality OR	95 % CI	p value	Adjusted H mortality OR	95 % CI	p value
Hospital mortality by geographic region						
N. America (REF)	1.00			1.00		
Asia	**1.29**	**0.80-2.06**	**0.29**	**1.22**	**0.69-2.14**	**0.49**
Oceania	0.52	0.11-2.51	0.41	0.28	0.03-2.67	0.27
W. Europe	1.10	0.71-1.70	0.69	0.98	0.58-1.66	0.94
E. Europe	2.47	1.41-4.31	0.001	2.46	1.27-4.77	0.008
C./S. America	1.77	1.05-3.00	0.033	2.17	1.16-4.03	0.015
Africa/M. east	1.69	0.88-3.22	0.11	1.33	0.61-2/86	0.47
Hospital mortality by Surviving Sepsis Campaign bundle compliance						
Full 3-h bundle	**0.60**	**0.45-0.80**	**<0.001**	**0.64**	**0.47-0.87**	**0.004**
Full 6-h bundle	**0.64**	**0.52-0.80**	**<0.001**	**0.71**	**0.56-0.90**	**0.005**

- **SSC bundle compliance is associated with hospital mortality.**

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

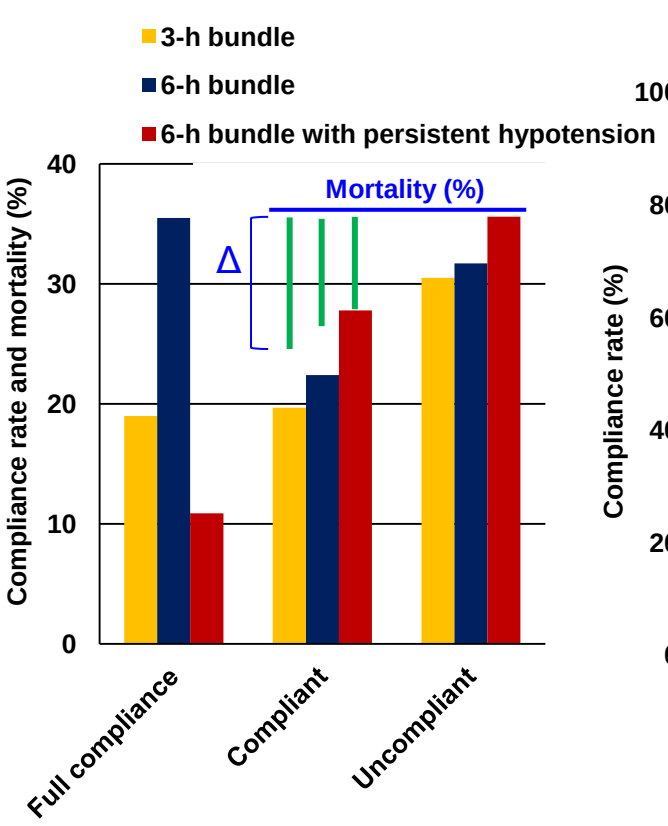
Results

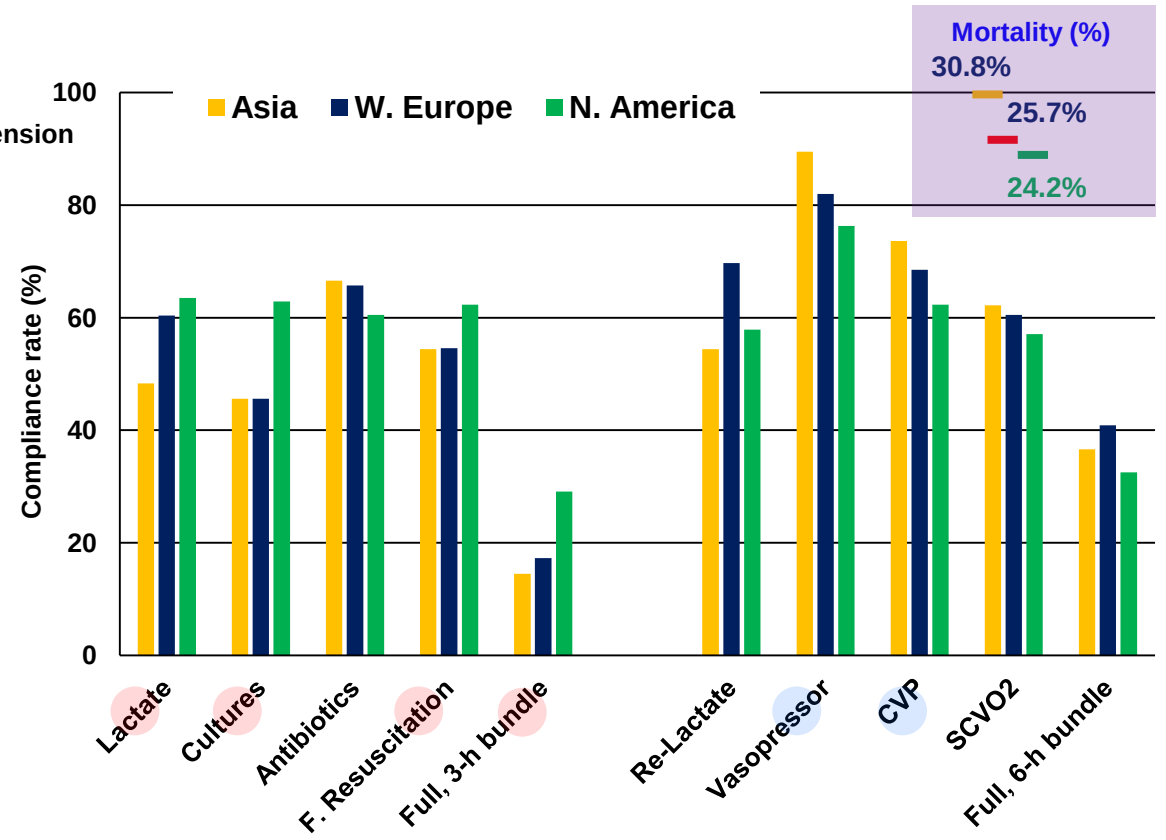
Surviving Sepsis Campaign bundle compliance and hospital outcome for patients			
Region, numbers	**Asia, 344**	**W. Europe, 623**	**N. America, 501**
3-h bundle compliance	N (%)	N (%)	N (%)
Measurement of lactate	166 (48.3)	376 (60.4)	318 (63.5)
Blood cultures before administration of antibiotics	157 (45.6)	284 (45.6)	315 (62.9)
Broad-spectrum intravenous antibiotics	229 (66.6)	409 (65.7)	303 (60.5)
Administer 30 mL/kg crystalloid for hypotension	187 (54.4)	340 (54.6)	312 (62.3)
Full bundle	**50 (14.5)**	**108 (17.3)**	**146 (29.1)**
Hospital mortality for 3-h bundle compliance	**7 (14.0)**	**19 (17.6)**	**32 (21.9)**
Hospital mortality for 3-h bundle noncompliance	**99 (33.7)**	**141 (27.4)**	**89 (25.1)**
6-h bundle compliance	N (%)	N (%)	N (%)
Repeat the lactate measurement	187 (54.4)	434 (69.7)	290 (57.9)
Application of vasopressors for hypotension	308 (89.5)	511 (82.0)	382 (76.3)
Measurement of central venous pressure	253 (73.6)	427 (68.5)	312 (62.3)
Measurement of $S_{CV}O_2$	214 (62.2)	377 (60.5)	286 (57.1)
Full bundle	**126 (36.6)**	**255 (40.9)**	**163 (32.5)**
Hospital mortality for 6-h bundle compliance	**34 (27.0)**	**52 (20.4)**	**29 (17.8)**
Hospital mortality for 6-h bundle noncompliance	**72 (33.0)**	**108 (29.3)**	**92 (27.2)**

Initial “3-h bundle compliance” may crucial point for survival.

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Results





Initial 3-h bundle compliance may direct associate with higher mortality

Emphasize the importance of early aggressive care for septic shock

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

SUMMARY

- Compliance with all of the evidence-based bundle metrics was not high.
- Patients whose care included compliance with all of these metrics had a 40 % reduction in the odds of dying in hospital with the 3-h bundle and 36 % for the 6-h bundle.

Compliance with SCC bundles improves outcome

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Comparison of some features of the Rivers, ProCESS, ARISE, and ProMISe studies

	Rivers et al.	ProCESS	ARISE	ProMISe
Inclusion years	1997-2000	2008-2013	2008-2014	2011-2014
No. control/EGDT groups	133/130	902/439	796/792	620/623
$ScvO_2$, % (EGDT group)	49	71	73	70
Lactate at inclusion (mEq/l)	7	5	4	5
Time from arrival at ED to randomization (min)	Median 55 (Mean 80)	Mean 190	Median 168	Median 162
Fluids administered before Randomization	20-30 ml/kg in 30 min (received NA)	≥20 ml/kg in 30 min, later >1000 ml (received 2200)	>1000 ml (received 2500)	>1000 ml (received 1600)
Antibiotics within 6 h (%)	89	97	100	100
Adequate antibiotics (%)	95 %	NA	90 %	NA
Achievement of goals in EGDT (%)	99.2	88.1	80 ($ScvO_2$ at 6 h)	85
Mortality control/EGDT (%)	50/33	19/21	19/19	29/29

Similar rate of early receipt of antibiotics, fluids and vasopressors and a high survival rate from severe sepsis and septic shock

Intensive Care Med DOI 10.1007/s00134-016-4295-6

Updated Bundles in Response to New Evidence

- **Not demonstrate superiority of required use of a CVC to monitor CVP and $ScvO_2$ in all patients with septic shock** who have received timely antibiotics and fluid resuscitation compared with controls or in all patients with lactate >4 mmol/L

SSC Executive Committee has revised the improvement bundles as follows:

3-h bundle

- Measure lactate level
- Obtain blood cultures prior to administration of antibiotics
- Administer broad spectrum antibiotics
- Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L

Revised 4/2015 by the SSC Executive Committee

6-h bundle

- Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a MAP ≥65 mmHg
- In the event of persistent hypotension after initial fluid administration (MAP <65 mm Hg) or if initial lactate was ≥4 mmol/L, **Re-assess volume status and tissue perfusion and document findings** according to Table.

EITHER
Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.
OR TWO OF THE FOLLOWING:
➢ **Measure CVP** ➢ **Measure ScvO2** ➢ **Bedside cardiovascular ultrasound** ➢ **Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge**

- Re-measure lactate if initial lactate elevated.

Summary of Sepsis-Related Issues

- Published RCTs of EGDT does not show improved survival.
- SSC Executive Committee has revised the 6-h bundle
  - Not enforced measurement of CVP and $ScvO_2$
  - Add in bedside CV ultrasound and dynamic assessment of fluid responsiveness
- Compliance with all of the evidence-based bundle metrics was not high.

CVP and $ScvO_2$, “two core components of the so-called EGDT sepsis bundle” may not necessary for all patients with septic shock

Abandoning sepsis protocols can lead to worse care

II.

Acute Respiratory Distress Syndrome And Acute Respiratory Failure

Epidemiology, Patterns of Care, and Mortality for Patients With ARDS in ICU in 50 Countries

"Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE)"

Objective

- **Primary**
  - ICU incidence of ARDS
- **Secondary**
  - Assessment of clinician recognition of ARDS
  - Application of ventilatory management
  - Adjunctive interventions in routine clinical practice
  - Clinical outcomes from ARDS

Methods

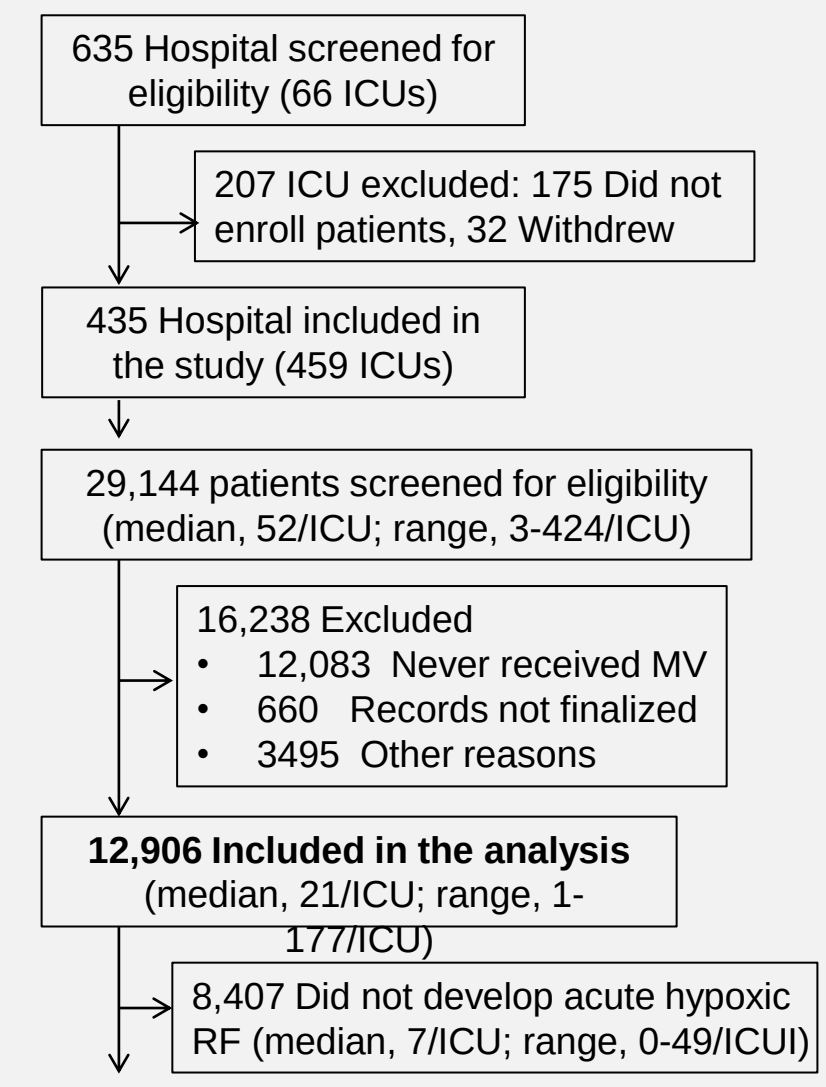
- Multicenter, prospective cohort study
- During 4 consecutive weeks in the winter of 2014
- 459 ICUs from 50 countries across 5 continents

JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

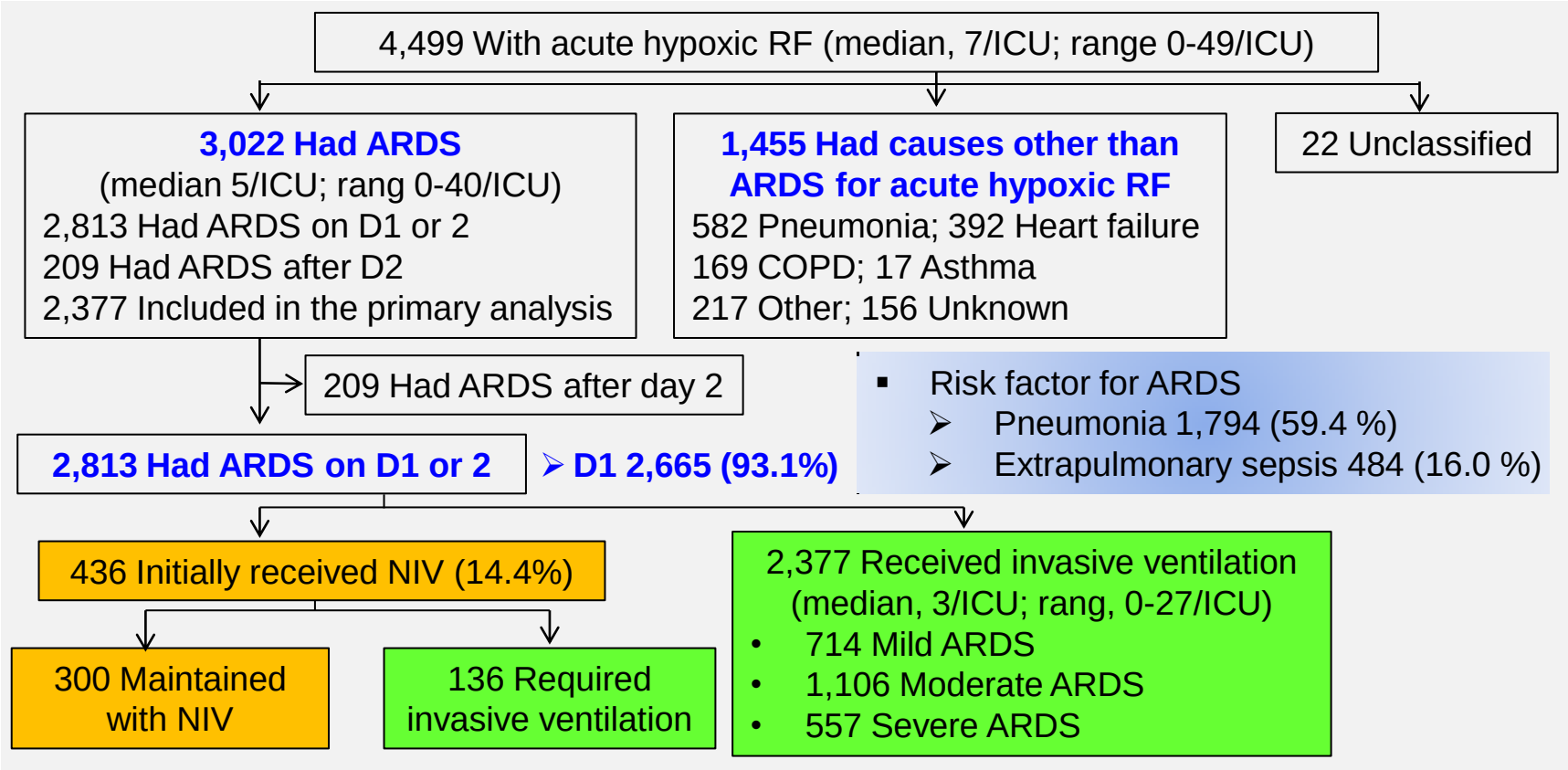
- Analyzed 12,906 patients
- Fulfilled ARDS criteria 3,022
- ARDS 10.4% of total ICU admissions
- 23.4% of all MV patients
- 0.42 cases/ICU bed over 4 weeks

Characteristics of participating ICUs	
Variable	Median [IQ]
Nurse/bed ratio (daytime)	0.67 [0.48-1.00]
Staff doctors/bed ratio (daytime)	0.25 [.12-.40]
Total doctors (staff, residents, fellows)/beds ratio (daytime)	0.50 [.35-.79



JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results



Recognized versus unrecognized ARDS

Extent of ARDS Recognition (n, %)	All (2377)	Mild (714, 30.0)	Moderate (1106, 46.5)	Severe (557, 23.4)	P value
ARDS Recognition at any time No. (%) (95% CI)	**1,525 (64.2)** (62.2-66.1)	366 (51.3) (47.5-55.0)	722 (65.3) (62.4-68.1)	437 (78.5) (74.8-81.8)	<0.001

JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

Organizational and Patient Factors Associated With Clinician Recognition of ARDS in Invasively Ventilated Patients

	Absolute Difference (95% CI)	Bivariate OR (95% CI)	P	Multivariable OR (95% CI)	P
No. of P/Dr, for each additional patient	−1.20 (−0.74 to −1.66)	0.960 (0.945-0.976)	<.001	0.959 (0.942-0.977)	<.001
No. of addit					02
Age, p					001
PBW					001
Nonpu per pc					001
P:F ra					001
Medic admis					11
Neopl hema					012
Pneumonia +	26.1 (22.2 to 30.0)	1.830 (1.544 to 2.170)	<.001	1.339 (1.073 to 1.670)	.01
Pancreatitis +	47.4 (36.9 to 58.0)	2.915 (1.436 to 6.733)	.006	3.506 (1.439 to 10.543)	.01
No ARDS risk factors	−29.1 (−36.3 to −22.0)	0.301 (0.220 to 0.408)	<.001	0.408 (0.280 to 0.591)	<.001
With heart failure	−15.6 (−21.2 to −10.0)	0.522 (0.415 to 0.657)	<.001	0.496 (0.377 to 0.652)	<.001

Higher probability of clinician recognition

- Higher nurse-to-patient ratios
- Higher physician-to-patient ratios
- Younger patient age
- Lower PaO_2/FIO_2 ratio
- Pneumonia or pancreatitis

JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

Effect of ARDS Recognition on Day 1 variables		
	Recog.	mean, (95% CI)
VT (ml/kg PBW)	ARDS +	7.5 (7.4-7.6)
	ARDS -	7.7 (7.6-7.9)
PEEP (cmH2O)	ARDS +	8.9 (8.8-9.1)
	ARDS -	7.5 (7.3-7.7)
P_{peak} (cmH2O)	ARDS +	28.3 (27.9-28.8)
	ARDS -	25.0 (24.5-25.6)
P_{plat} measured	ARDS +	648 (42.5%) (40.0-45.0)
	ARDS -	280 (32.9%) (29.7-36.1)
P_{plat} (cmH2O)	ARDS +	24.4 (23.9-24.9)
	ARDS -	20.6 (19.9-21.3)
VE (l/min)	ARDS +	11.0 (10.8-11.3)
	ARDS -	10.4 (10.0-10.7)
Use of adjunctive	ARDS +	670 (43.9%) (41.4-46.5)
	ARDS -	185 (21.7%) (19.0-24.6)

ARDS recognized

- Lower VT
- Higher PEEP, airway pressure, and VE
- Higher rate of using adjuctive management

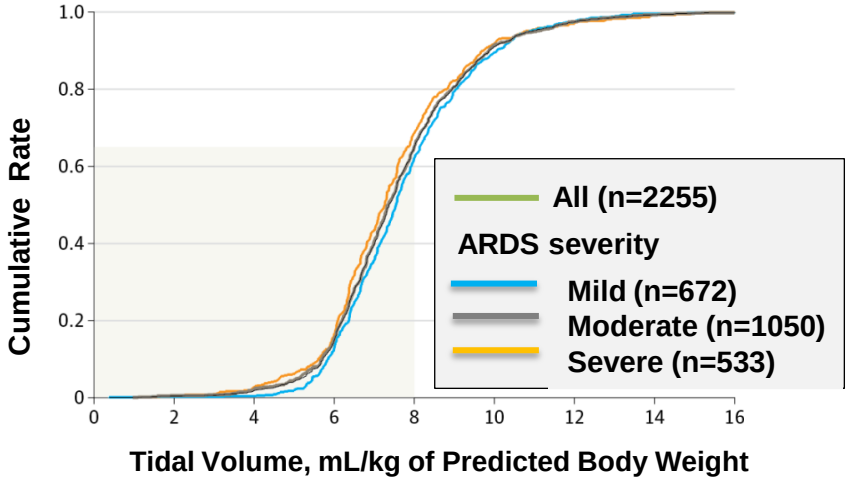
JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

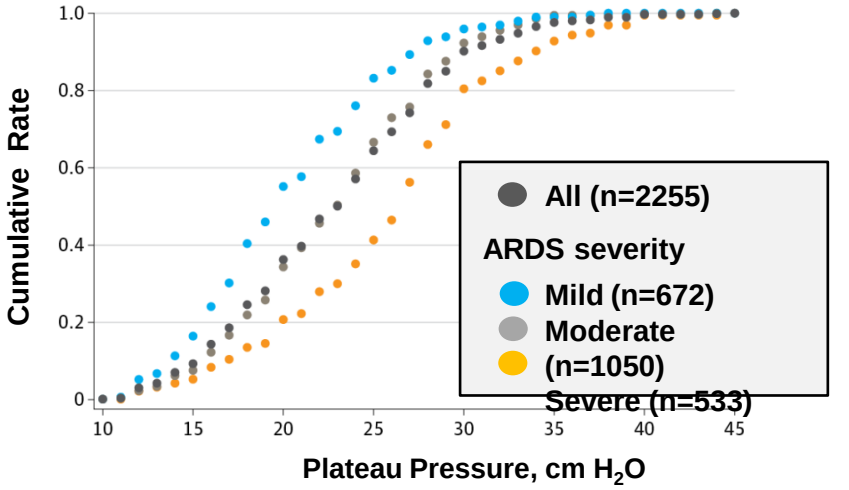
- Similar tidal volume distribution
- VT > 8 mL/kg PBW 35.1%
- PEEP ≤12 cm H_2O 82.6%

- Right shift of the cumulative frequency distribution of P_{plat} with ARDS severity
- P_{plat} > 30 cm H_2O 8.5%

Cumulative frequency distribution of tidal volume



Cumulative frequency distribution of plateau pressure

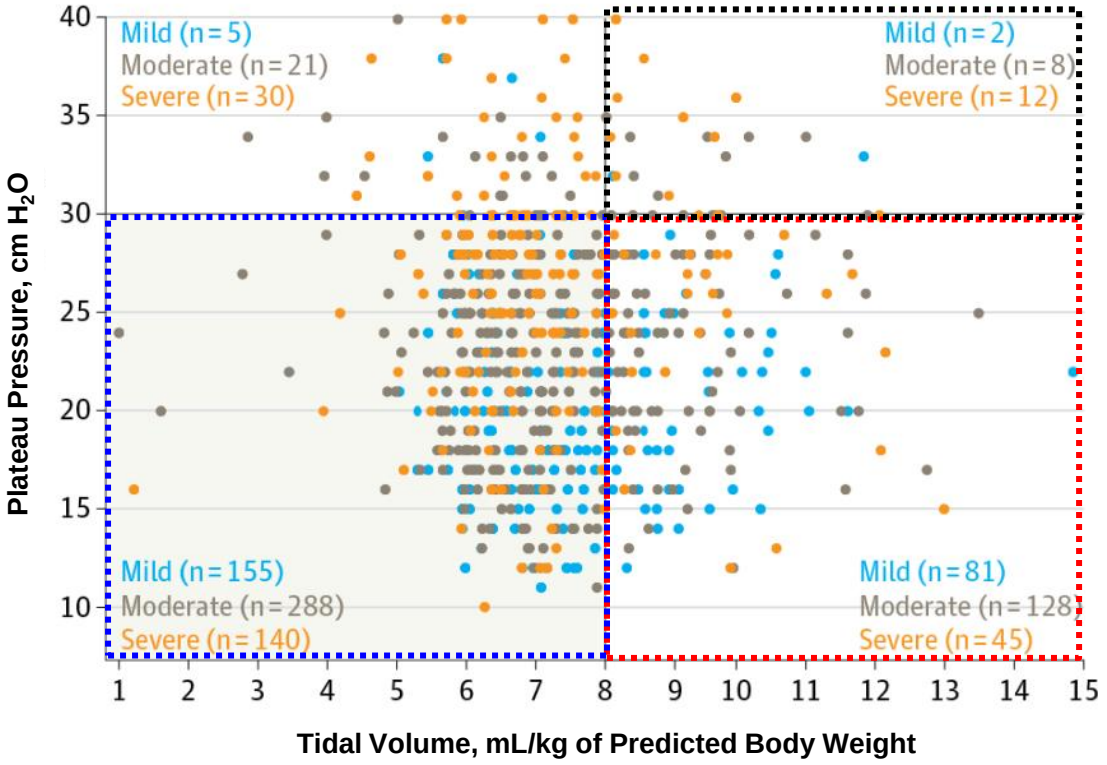


JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

- Protective mechanical ventilation 2/3
- VT >8 mL/kg PBW: P_{plat} <30 cm H_2O 91.9%, P_{plat} >30 cm H_2O <3%

Distribution of VT vs. P_{plat} on D1 by ARDS severity



JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With ARDS					
	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild (n = 498)	Moderate (n = 1150)	Severe (n = 729)	*P*
NM blocker	516 (21.7) [20.1-23.4]	**34 (6.8) [4.8-9.4]**	**208 (18.1) [15.9-20.4]**	**274 (37.8) [34.1-41.2]**	<.001
Re ma					<.001
Pr					<.001
EC					<.001
Inh					<.001
HF					.347
No ab					<.001
EP					.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
Corticosteroids	425 (17.9) [16.4-19.5]	**61 (12.3) [9.5-15.5]**	**194 (16.9) [14.7-19.2]**	**170 (23.3) [20.3-26.6]**	<.001
PA catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

Continuous NMB, corticosteroids, and ARM were the most frequently used adjuncts.

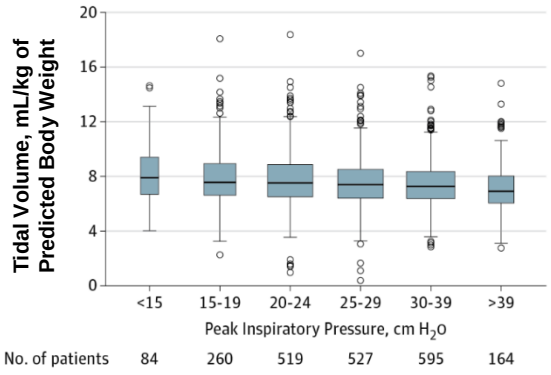
Patients with severe ARDS

- Prone position 16.3%, 95% CI [13.7-19.2]
- ECMO 6.6%, 95% CI [4.9-8.6]
- Corticosteroids 23.3%, 95% CI [20.3-26.6]

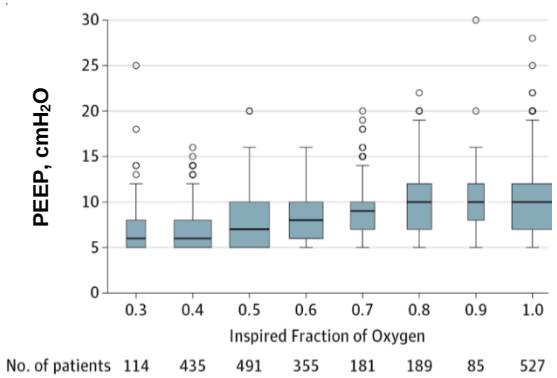
JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

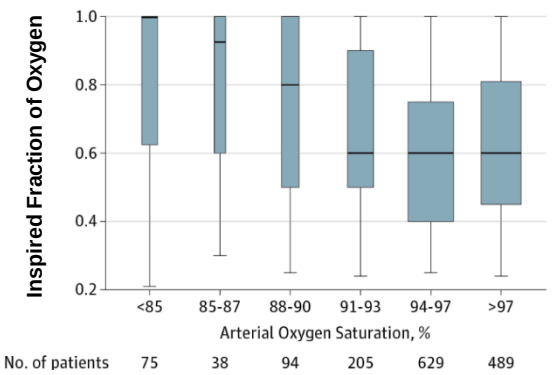
Relationship between tidal volume and peak inspiratory pressures



Relationship between PEEP and inspired fraction of oxygen



Relationship between inspired fraction of oxygen and SaO2

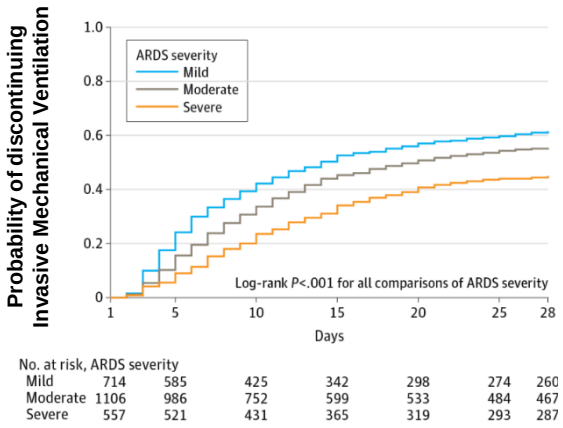


- VT remained relatively constant across the range of PiP.
- PEEP progressively increased in patients requiring higher FIO_2.
- Stepwise increase in FIO_2 at lower SaO_2, with FIO_2 steeply increasing at SaO_2 ≤91%.

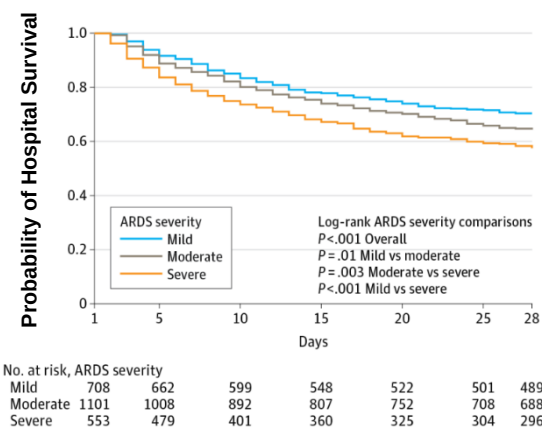
JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

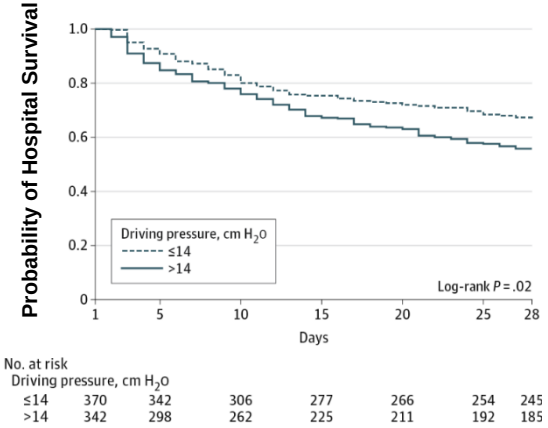
Probability of discontinuing MV by ARDS severity



Probability of hospital survival by ARDS severity



Probability of hospital survival by driving pressure

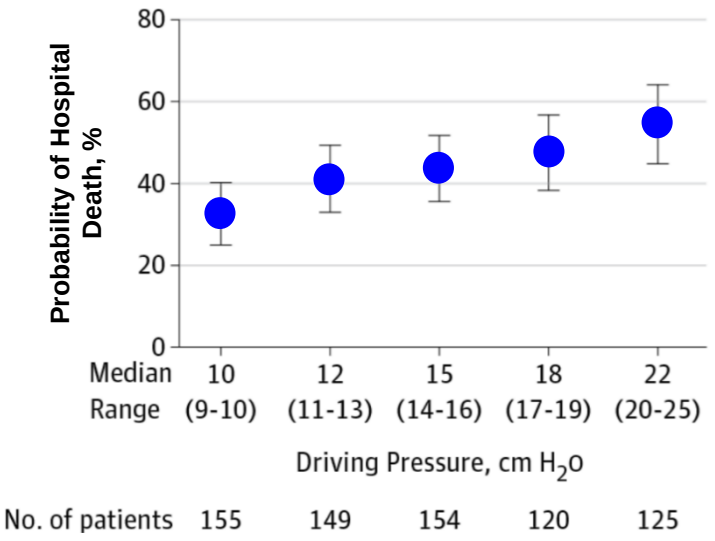


- Lower likelihood of UAB with increasing severity of ARDS.
- Lower likelihood of survival to D28 with increasing severity of ARDS at D1.
- Patients with a driving pressure of greater than 14 cm H_2O on D1 of ARDS criteria had a higher mortality.

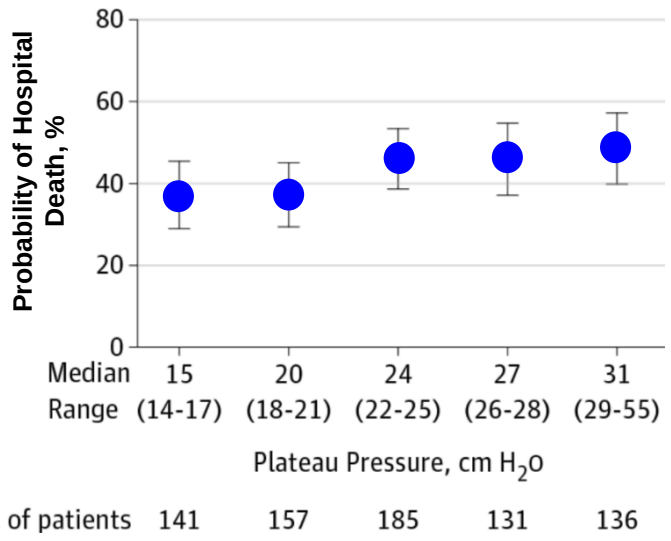
JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Results

Driving pressure quintiles and risk of hospital death



Plateau pressure quintiles and risk of hospital death



Direct relationship between both plateau and driving pressure quintile and mortality rate on D1 of ARDS.

JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Summary

- Prevalence of ARDS was 10.4% of ICU admissions
  - 23.4% of all MV patients
  - 0.42 cases/ICU bed over 4 weeks
- Very high mortality ≒ 40%

- Under recognition of ARDS
- Low use of contemporary ventilatory strategies and adjuncts

Potential for improvement in management of patients with ARDS

- **Early recognition**
- **Prompt adjuncts with Lung protective MV strategies**

JAMA. 2016;315(8):788-800. doi:10.1001/jama.2016.0291

Prolonged Glucocorticoid Treatment Is Associated With Improved ARDS Outcomes: Analysis Of Individual Patients' Data From Four Randomized Trials And Trial-level Meta-analysis Of The Updated Literature

Objective

- To investigate the effect of prolonged glucocorticoid treatment for patients with ARDS

Methods

- 4 RCTs methylPD treatment (n = 322) and 4 additional RCTs hydrocortisone treatment in early ARDS (n = 297)

- **Primary outcome**
  - ➢ Time to achieving unassisted breathing (UAB) by study D28
- **Secondary outcomes**
  - ➢ MV & ICU-free D, hospital mortality, and time to hospital mortality by D28

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Dose and duration of methylprednisolone or hydrocortisone

	Placebo, number	Gluco-corticoide, number	Total dose (mg) D1-7 methylPD	Total hydro-cortisone equivalents (mg) D1-7	Maximum duration of steroid therapy (days)
Intravenous dosing strategy for methylprednisolone studies					
Meduri et al, 1998	8	14	1120	5600	31
Steinberg et al. 2006	92	85	1120	5600	25
Meduri et al. 2007	28	63	560	2800	28
Rezk et al. 2013	9	18	560	2800	28
Intravenous dosing strategy for hydrocortisone studies					
Confaloneri et al. 2005	19	15		1880	7
Annane et al. 2006	66	66		2100	7
Sabry et al. 2011	34	26		2100	7
Liu et al. 2012	14	12		2100	7

Protocols of methylprednisolone or hydrocortisone treatment

Intravenous dosing strategy for methylprednisolone studies	
Meduri et al, 1998	**Loading 2 mg/kg** → 2 mg/kg/D (D1-4) →1 mg/kg/D (D15-21) → 0.5 mg/kg/D (D22-28) → 0.25 mg/kg/D (D 29-30) → 0.125 mg/kg/D (D30-31)
Steinberg et al. 2006	**Loading 2 mg/kg** → 0.5 mg/kg of PBW every 6 h for 14 D → 0.5 mg/kg of PBW every 12 h for 7 D → tapering Study drug was tapered over a period of 4 D if D days of treatment had been completed and the patient was unable to breathe without assistance for a period of 48 h.
Meduri et al. 2007	**Loading 1 mg/kg** → 1 mg/kg/D (D1-14) → 0.5 mg/kg/D (D15-21) → 0.25 mg/kg/D (D 22-25) → 0.125 mg/kg/D (D 26-28). If the patient was extubated between D1 and D14, the patient was advanced to D15 of drug therapy and tapered according to schedule.
Rezk et al. 2013	**Load 1 mg/kg** → 1 mg/kg/D (D1-14) → 0.5 mg/kg/D (D15-21) → 0.25 mg/kg/D (D22-25) → 0.125 mg/kg/D (D26-28)

Intravenous dosing strategy for hydrocortisone studies	
Confaloneri et al. 2005	200 mg bolus then 10 mg/h for 7 days
Annane et al. 2006	50 mg hydrocortisone every 6 h and 50 mcg fludrocortisone for 7 days
Sabry et al. 2011	12.5 mg/h hydrocortisone for 7 days
Liu et al. 2012	100 mg hydrocortisone, three times per day for 7 days

Results

Effects of prolonged methylprednisolone treatment on secondary outcomes based on individual patient data from four randomized clinical trials of ARDS

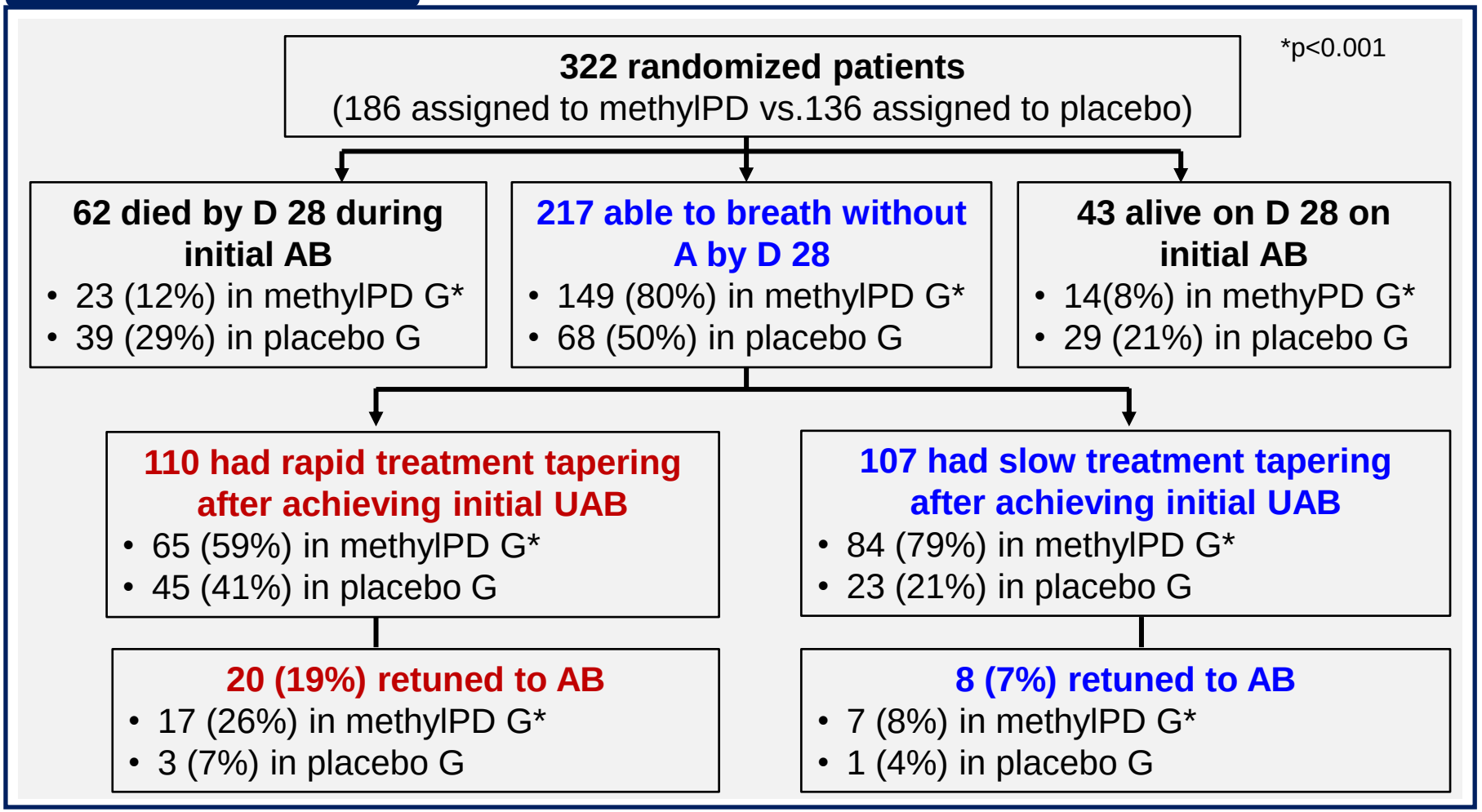
Outcome variables	MethylPD (N = 186)	Placebo (N = 136)	OR (95 % CI) or LSD between means (95 % CI)
Died			1
Alive			03
Hosp			6
Hosp before			1
Achie			1
Retur			15
Mech			01
Duration of initial AB (+ data past D 28)	12.9±13.4	23.0±13.9	-10.10 (-13.12-7.08), p<0.001
Shock after study entry	6 (3%)	20 (15%)	0.25 (0.097-0.658), p<0.001
Patients with new infection after study entry	59 (32%)	56 (41%)	0.52 (0.311-0.857), p=0.011
Discharged alive from the ICU by D 28	139 (75%)	66 (49%)	2.92 (1.802-4.72), p<0.001
Re-admission to ICU by D 28	21 (11%)	4 (3%)	4.84 (1.60-14.64), p=0.050
ICU: free D up to D 28	10.8±0.71	6.4±0.85	4.45 (2.64-6.26), p<0.001
Hospital: free D up to D 28	7.0±0.57	3.82±0.68	3.19 (1.74-4.64), p<0.001

Methyprednisolone group

- Earlier unassisted breathing
- Lower hospital mortality
- Not associated with increased risk for infections
- Higher ICU and hospital free days

Intensive Care Med DOI 10.1007/s00134-015-4095-4

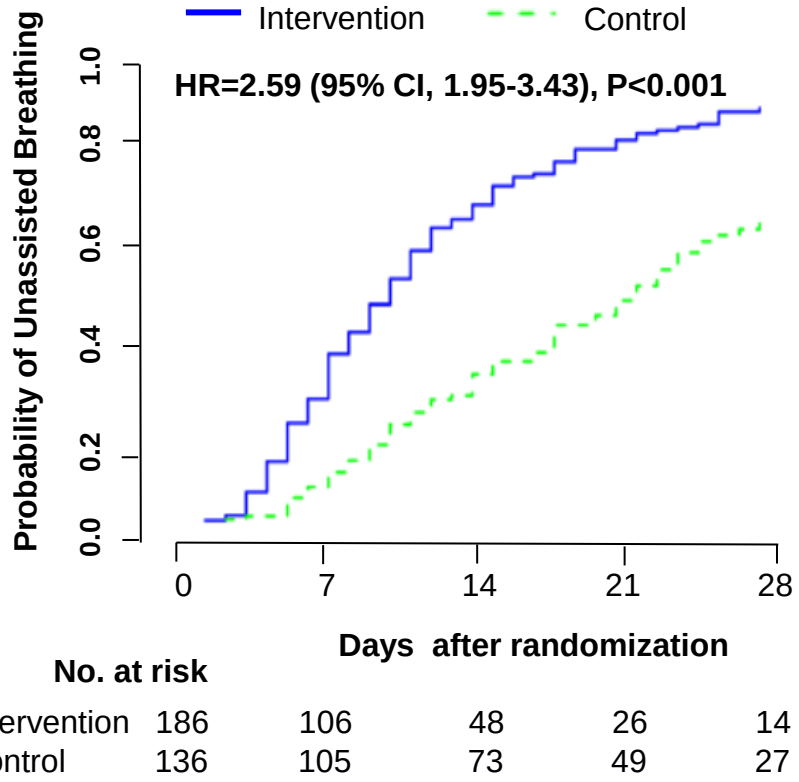
Results



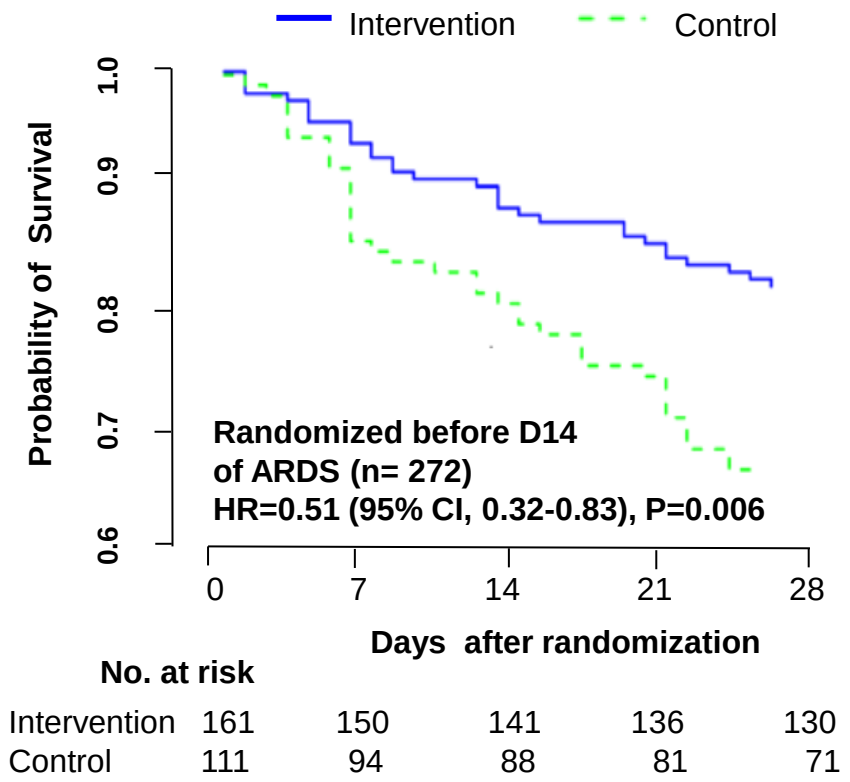
Rapid treatment tapering after achieving initial UAB resulted in return to assisted breathing.

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Results



Probability of achieving UAB from randomization to hospital discharge or D28.



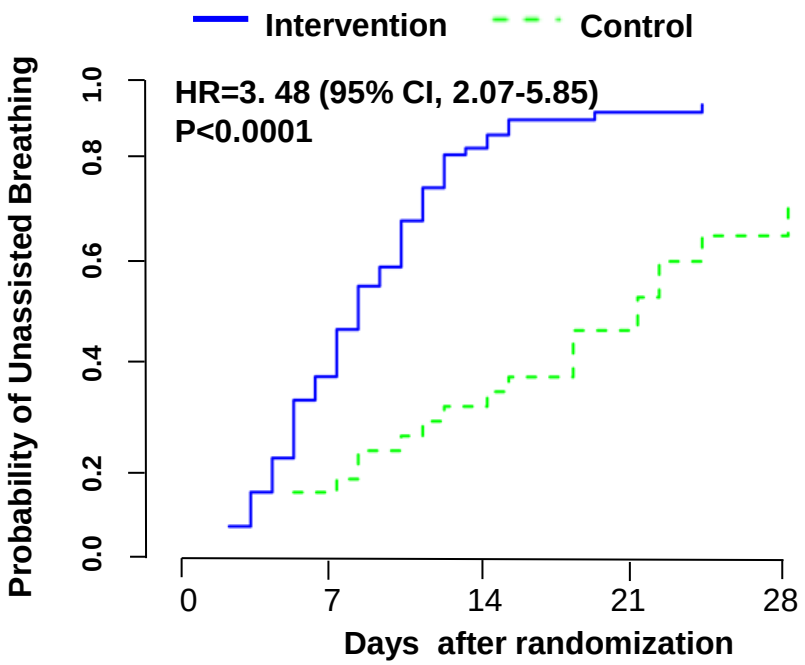
Probability of survival from randomization to hospital discharge or D28.

- By D28, the methylPD group achieved initial UAB earlier.
- The probability of death by hospital discharge or D28 for patients with ARDS randomized before D14 of ARDS onset.

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Results

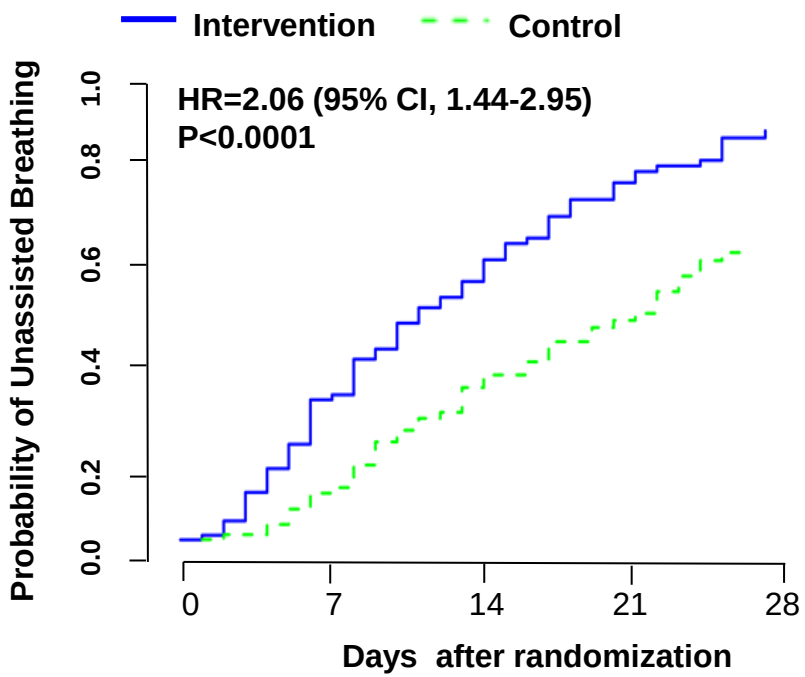
A. Early initiation



No. at risk

Intervention	81	40	7	4	3
Control	37	28	21	12	5

B. Late initiation



No. at risk

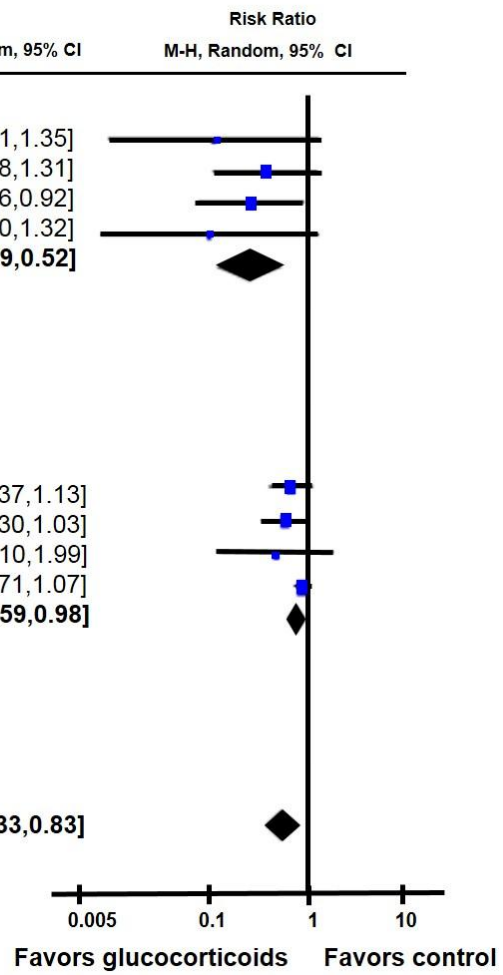
Intervention	105	68	41	22	11
Control	99	77	52	37	22

Initiation of treatment (early vs. late) was not associated with time to achieve UAB or time to death by hospital discharge or day 28.

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Results

Study or Subgroup	Glucocorticoids Events	Total	Control Events	Total	Risk Ratio Weight	M-H, Random, 95% CI
1.1.1 Less than 60 patients						
Confalonieri, 2005	0	15	7	19	2.5%	0.08[0.01,1.35]
Liu, 2012	2	12	7	14	8.3%	0.03[0.08,1.31]
Meduri, 1998	2	14	5	8	8.1%	0.23[0.06,0.92]
Rezk, 2013	0	18	3	9	2.4%	0.08[0.00,1.32]
Subtotal (95% CI)		**59**		**50**	**21.3%**	**0.22[0.09,0.52]**
Total events	4					
Heterogeneity: Tau^2=0.00; Chi^2=1.47, df=3 (p=0.69); I^2=0%						
Test for overall effect:Z=3.41 (P=0.0006)						
1.1.2 More than 60 patients						
Annane, 2006	15	66	23	66	21.6%	0.65[0.37,1.13]
Meduri, 2007	15	63	12	28	20.2%	0.56[0.30,1.03]
Sabry, 2011	2	26	6	34	7.1%	0.44[0.10,1.99]
Steinberg, 2006	54	85	67	92	29.7%	0.87[0.71,1.07]
Subtotal (95% CI)		**240**		**220**	**78.7%**	**0.76[0.59,0.98]**
Total events	86		108			
Heterogeneity: Tau^2=0.02; Chi^2=3.62, df=3 (0.31); I^2=17%						
Test for overall effect: Z=2.11 (P=0.03)						
Total(95% CI)		**299**		**270**	**100.0%**	**052[0.33,0.83]**
Total events	90		130			
Heterogeneity:Tau^2=0.17; Chi^2=15.64, df=7(P=0.03); I^2=55%						
Test for overall effect: Z=2.75 (P=0.006)						
Test for subgroup differences: Chi^2=7.23, df=1(P=0.007), I^2=86.2%						



Prolonged methylprednisolone treatment decreasing hospital Mortality.

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Summary

- Prolonged low-dose methylprednisolone treatment initiated early in ARDS and incorporating slow tapering to prevent rebound inflammation is associated with improved ARDS outcomes
  - Reduces duration of MV
  - Reduces mortality without increased rate of infections

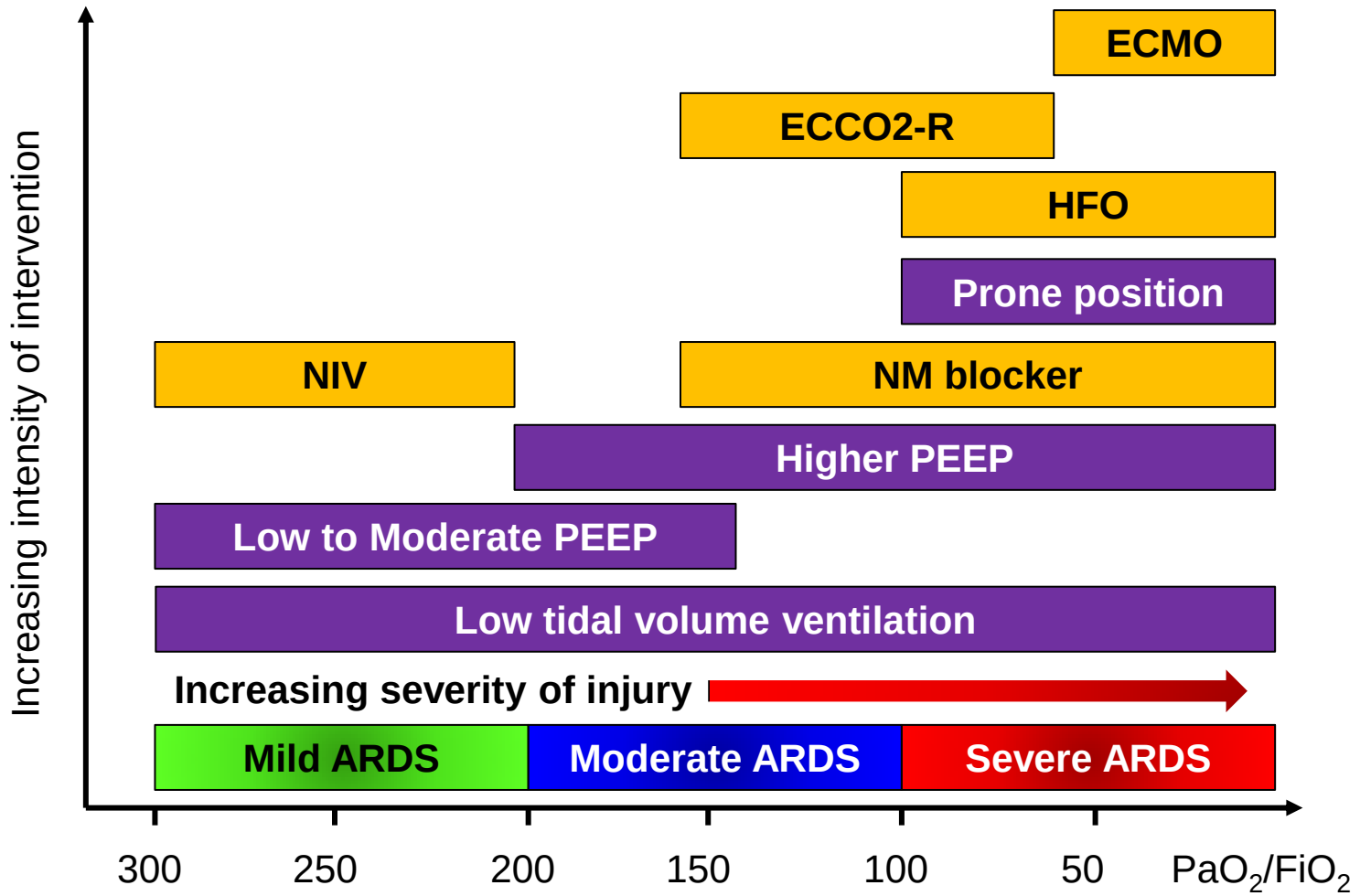
Rapid tapering after achieving initial UAB led to greater return to AB with partial loss of early survival benefits

Glucocorticoids in severe ARDS - early, low-dosed, and prolonged - act as an important part of the management bundle.

Intensive Care Med DOI 10.1007/s00134-015-4095-4

Aligning Therapeutic Options with The Berlin Definition

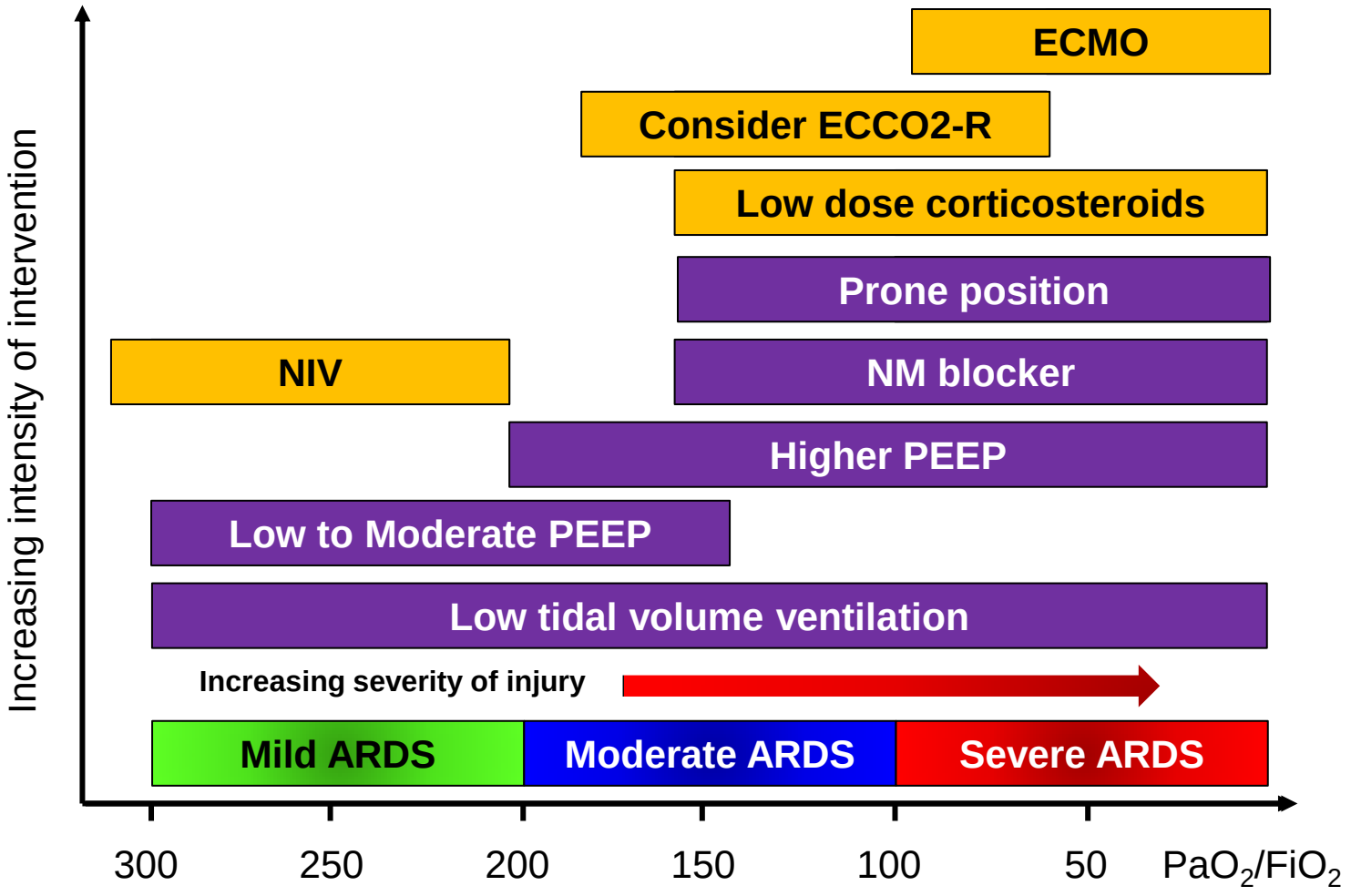
Potential therapeutic options according to the severity of ARDS



The Berlin definition of ARDS. An expanded rationale, justification, and supplementary material. Intensive Care Med (2012) 38:1573–1582 DOI 10.1007/s00134-012-2682-1

Aligning Revised Therapeutic Options with The Berlin Definition

Potential therapeutic options according to the severity of ARDS



T Bein, et al.Intensive Care Med DOI 10.1007/s00134-015-4162-x

Summary of ARDS-Related Issues

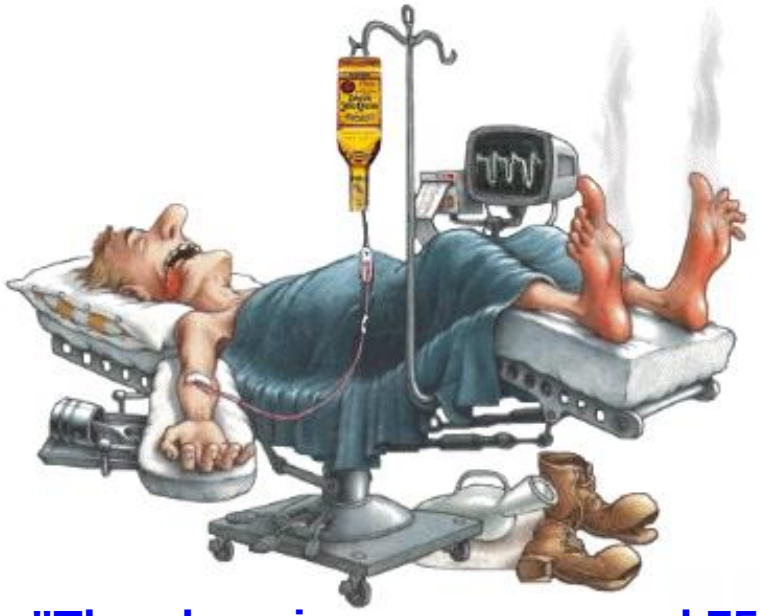
- The management of ARDS should incorporate with lung protective ventilation, adequate PEEP, prone positioning, early and low-dose glucocorticoids (methylprednisolone initially 1 mg/kg/day, then dose tapering), and a short course of a short-acting neuromuscular blocker.

One treatment strategy may not fit all patients fulfilling the clinical criteria of ARDS

Revised Therapeutic Options with The Berlin Definition

Potential therapeutic options according to the severity of ARDS

“Medicare Plan G – Nursing Home Plan”



Let's say you are an older senior citizen who can no longer take care of yourself.

But the government says there is no Nursing Home care available for you.

So, what do you do? You should opt for “Medicare Plan G”.

"The plan gives anyone aged 75 or older a gun (Plan G) and one bullet”.

You are allowed to shoot one worthless politician!

This means you will be sent to prison for the rest of your life. There you will receive three meals a day, a roof over your head, central heating, air conditioning, cable TV, a library, and all the Health Care you need.

Need new teeth? No problem. Need glasses? That's great. Need a hearing aid, new hip, knees, kidney, lungs, sex change, or heart?

They are all covered! As an added bonus, your kids can come and visit you at least as often as they do now!

And, who will be paying for all of this? The same government that just told you they can't afford for you to go into a nursing home.

And you will get rid of a useless politician while you are at it. And now, because you are a prisoner, you don't have to do HMRC (Her Majesty Revenue and Customs) returns or pay any more income taxes!

Is this a great country or what?

Now that I've solved your senior financial plan, enjoy the rest of your week!

Fluid Challenges in Intensive Care: The FENICE Study
A Global Inception Cohort Study

Objective

- **Primary**
  - To evaluate how physicians conduct FCs: type, volume, and rate
- **Secondary**
  - To evaluate variables used to trigger an FC
  - To compare the proportion of patients receiving further fluid administration based on the response to the FC

Methods

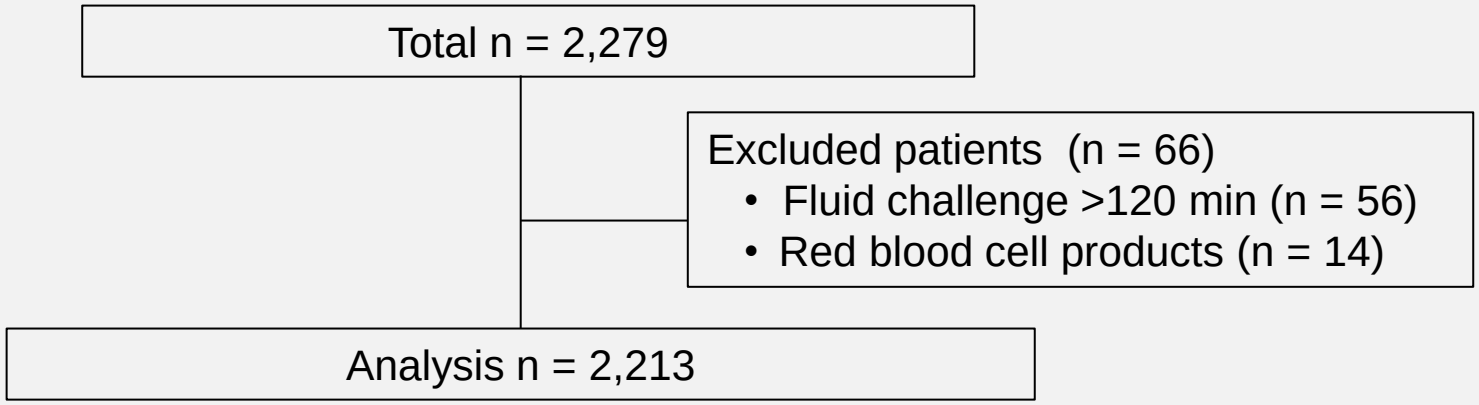
- Observational Global study, maximum of 20 patients/unit

- **Fluid challenge (FC)**
  - Administration of any bolus of fluid (crystalloid or colloid) < 2 h
  - Exclude administration of RBC or FFP

- Only one FC, ideally the first, was considered for each patient
- Only one FC per patient was recorded

Intensive Care Med (2015) 41:1529–1537 DOI 10.1007/s00134-015-3850-x

Results



- **Main diagnostic groups**
  - Sepsis (27.0 %), cardiac failure (20.6 %), respiratory failure (10.8 %)
- **Median amount, time, and rate**
  - 500 ml (500-1000), 24 min (40-60 min), and 1000 (500-1333) ml/h
- **Fluid type**
  - Crystalloids 74.0 % [CI 72.2-75.8 %]
    - ✓ NS 45.9 %, balanced solutions 53.5 %

Intensive Care Med (2015) 41:1529–1537 DOI 10.1007/s00134-015-3850-x

Results

Indications used to predict fluid responsiveness (N = 2,213)	
Hypotension	1,211 (58.7 [56.7–60.8])
Weaning vasopressor	146 (7.1 [6.0–8.2])
Cardiac output	62 (3.0) [2.3–3.7]
Oliguria	372 (18.0 [16.4–19.6])
Skin mottling	36 (1.7 [1.2–2.2])
Lactate	128 (6.2 [5.2–7.2])
$SvO_2/ScvO_2$	10 (0.5 [0.2–0.8])
SVV/PPV	37 (1.8 [1.3–2.4])
CVP/PAOP	60 (2.9 [2.2–3.6])

The main indication for fluid administration was hypotension.

Intensive Care Med (2015) 41:1529–1537 DOI 10.1007/s00134-015-3850-x

Results

Variables used to predict fluid responsiveness (N = 2,213)			
	n	% of category	% All
No variable used	945		42.7 [40.6–44.8]
Any variable used	1268		57.3 [55.2–59.4]
Static	785		35.5 [33.5–37.5]
CVP	572	89.9 [87.8–92.0]	25.8 [24.0–27.6]
Dynamic	488		21.6 [20.2–23.0]
Pulse pressure variation	88	18.2 [14.8–21.6]	4.0 [3.2–4.8]
Stroke volume variation	88	18.2 [14.8–21.6]	4.0 [3.2–4.8]
PPV + SVV	24	5.0 [3.1–6.9]	1.1 [0.7–1.5]
Passive leg raising	238	49.3 [44.8–53.8]	10.7 [9.4–12.0]
Echo variables	45	9.3 [6.7–11.9]	2.0 [1.4–2.6]

CVP: Poor variable to predict fluid responsiveness

Marik PE, et al. Crit Care Med. 2014; 41:1774–1781

PLR: Inaccuracy in cardiac output and stroke volume

Monnet X, et al. Crit Care Med. 2006; 34:1402–1407

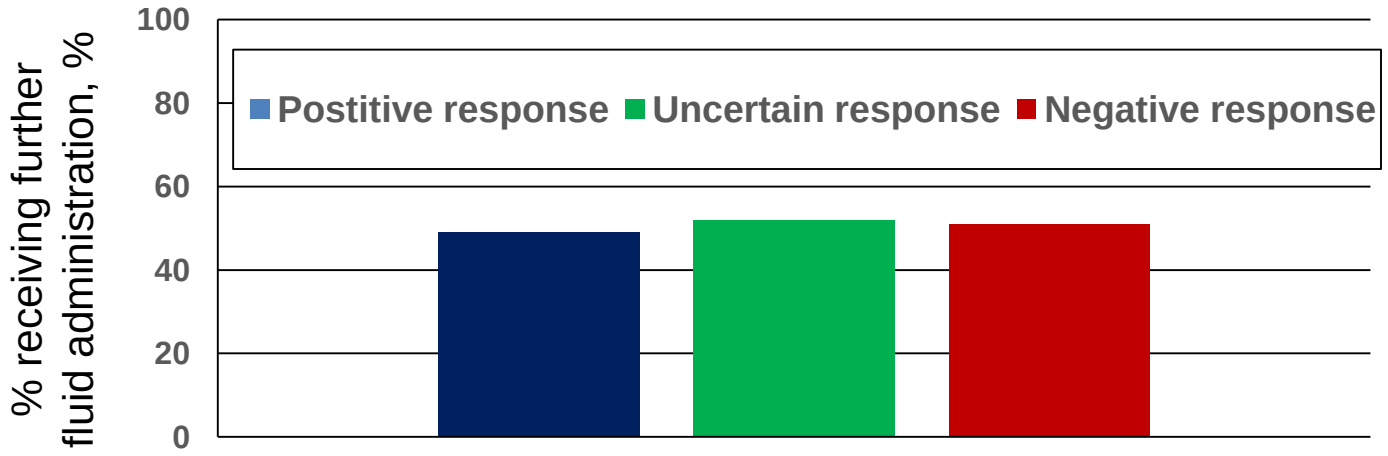
Intensive Care Med (2015) 41:1529–1537 DOI 10.1007/s00134-015-3850-x

Results

Judged response to fluid challenge			
Response classification [no. (%) of 2,162]			
Negative response	429 (19.8 [18.1–21.5])		
Positive response	1544 (71.4 [69.5–71.4])		
Variable use to evaluate response [no. (%) of 1,544 with positive response]		Safety limit used [no. (%) of 2,213]	577 (27.9 [25.7–30.1])
Increase in BP	1039 (67.3 [65.0–69.7])		
Decrease vasopressors	56 (3.6 [2.7–4.5])	**Variable used in the safety limit group [no. (%) of 577]**	
Increase in CO	174 (11.3 [9.7–12.9])	CVP	329 (57.0 [53.0–61.0])
Increase in SV	100 (6.5 [5.3–7.7])	PAOP	39 (6.7 [4.7–8.8])
Decrease in HR	374 (24.2 [22.1–26.3])	GEDVI	11 (1.9 [4.7–8.8])
Urine output	590 (38.2 [35.8–40.6])	EVLWI	28 (4.9 [3.1–6.7])
Lactate	281 (18.2 [16.3–20.1])	SpO_2/SaO_2	105 (18.2 [15.1–21.35])
Skin perfusion	128 (8.3 [6.9–9.7])	CO	8 (1.4 [0.4–2.4])
Mental state	40 (2.6 [1.8–3.4])	SVV/PPV	80 (13.9 [11.1–16.7])
$ScvO_2/SvO_2$	77 (5.0 [3.9–6.1])	Other	120 (20.8 [17.5–24.1])
SVV/PPV	110 (7.1 [5.8–8.4])		
CVP/PAOP	256 (16.6 [14.7–18.5])		
Other	132 (8.5 [7.1–9.9])		

Intensive Care Med (2015) 41:1529–1537 DOI 10.1007/s00134-015-3850-x

Results



Further fluid administration post FC, n (%)	1,050 (47.4 ± 2.5)	OR
with an initial positive response, n (%)	739 (47.9 ± 2.5)	Ref
with an initial negative response, n (%)	212 (49.4 ± 6.6)	0.94 (0.76-1.16)
with an initial uncertain response, n (%)	99 (52.4 ± 7.1)	0.83 (0.62-1.13)

Proportion of receiving further fluids after FC
"Positive response ≅ Uncertain response ≅ Negative response"

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Summary

- Significant variability in the conduction of FC
- Simple clinical signs led to FC (> 80 % patients)
  - Hypotension, oliguria, or weaning of vasopressors
- Markers of inadequate tissue perfusion ≤8 %
- The response to the initial FC does not have an impact when prescribing further fluid administration.

MAP = (CO x SVR) + CVP

More standardized approach to a FC could lead to better patient-centered outcomes

Intensive Care Med (2015) 41:1620–1628 DOI 10.1007/s00134-015-3906-y

Changing Use Of Noninvasive Ventilation In Critically Ill Patients: Trends Over 15 Years In Francophone Countries

Objective

- Current trends in NIV use

Methods

- Comparison in 1997, 2002, and 2011 in francophone countries

Carlucci A, et al. Am J Respir Crit Care Med. 2001; 163:874–880
Demoule A, et al. Intensive Care Med. 2006; 2:1747–1755

- Multicenter prospective audit and a comparative study
- Over a 2-month period between November 2010 and April 2011

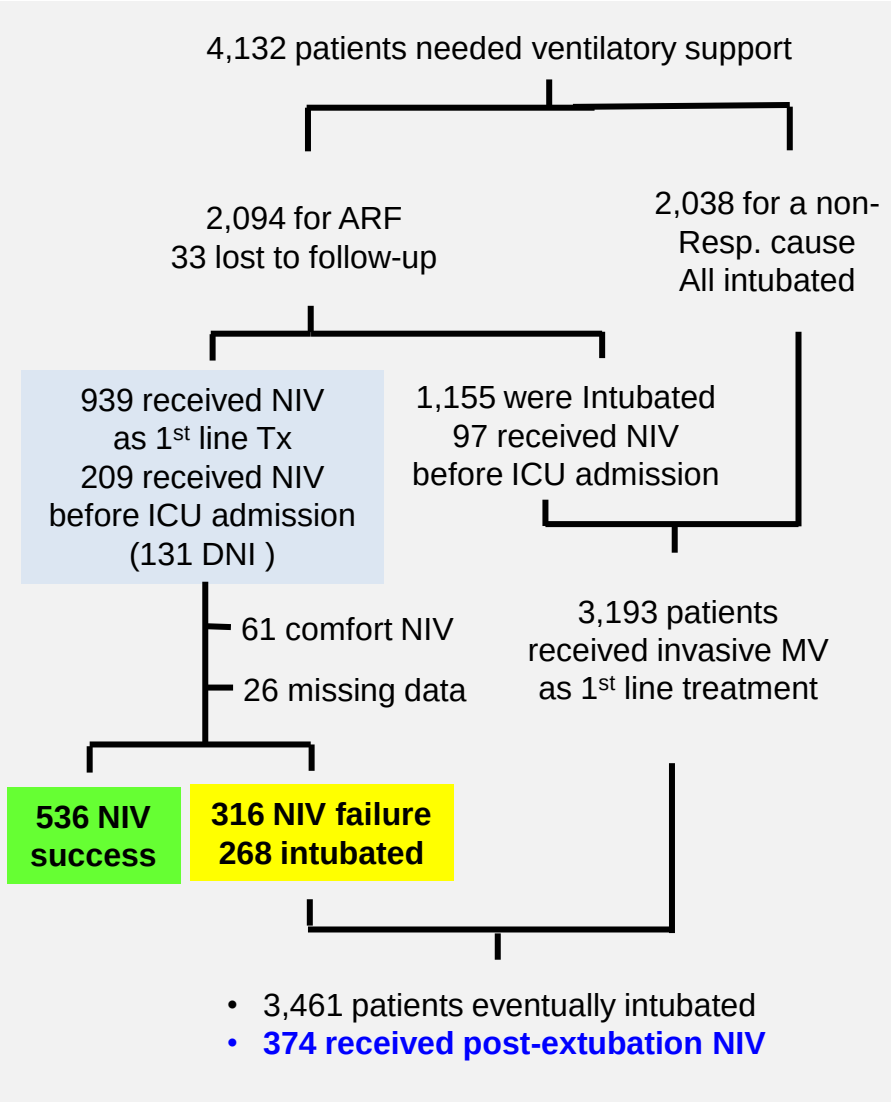
Intensive Care Med (2016) 42:82–92 DOI 10.1007/s00134-015-4087-4

Results

Main characteristics of participating ICU in the three prospective audits and reasons for ventilatory support

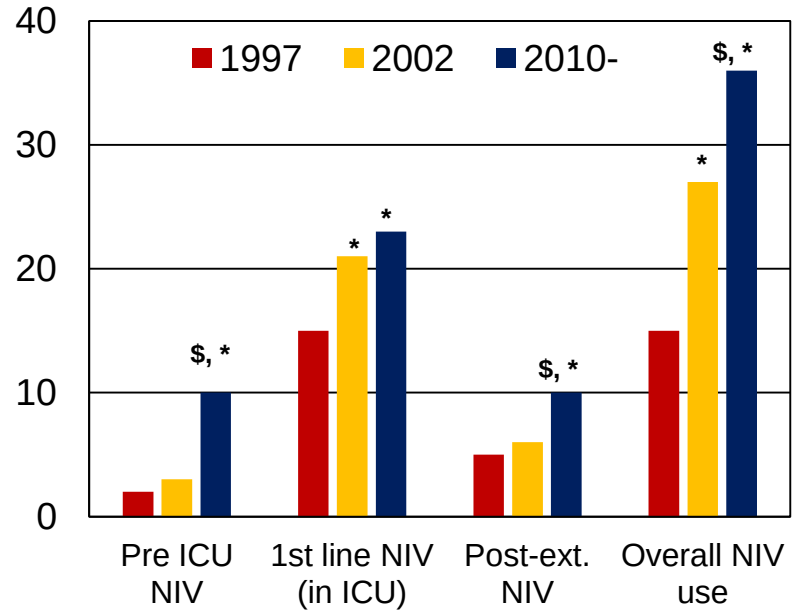
	1997	2002	2010/11
Total No.	689	1076	2367
MV for ARF	361 (52)	588 (55)	1145 (48) $
Acute-on-CRF	85 (12)	167 (16)	467 (20)*,$
COPD	63 (9)	114 (11)	320 (14)
Restrictive dis.	22 (3)	46 (4)	147 (6)
Acute cardio. PE	49 (7)	84 (8)	140 (6)
De novo ARF	227 (33)	337 (31)	538 (23)*,$
Pneumonia	95 (14)	163 (15)	360 (15)
Ext-pulm sepsis	49 (7)	65 (6)	62 (3)
Other	49 (7)	65 (6)	62 (3)
MV, No-Resp.	328 (48)	488 (45)	1222 (52) $
Coma	201 (29)	358 (33)	719 (30)
PostOP Mx.	103 (15)	130 (12)	240 (10)
Other	24 (3)		263 (11)

* P<0.05 vs. 1997; $ P<0.05 vs. 2002

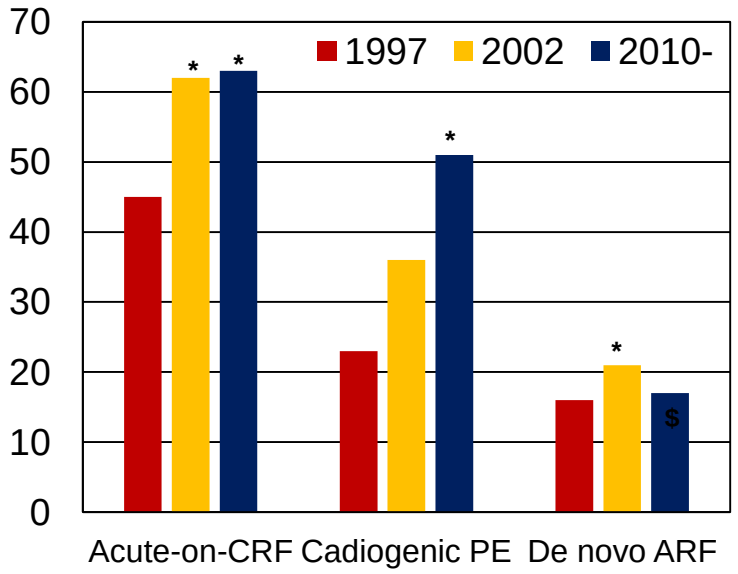


Intensive Care Med (2016) 42:82–92 DOI 10.1007/s00134-015-4087-4

Results



Changes in the use of NIV across the three study periods. *P <0.05 compared to 1997, $P< 0.05 compared to 2002



Changes in the use of NIV according to the cause of ARF. . *P <0.05 compared to 1997, $P< 0.05 compared to 2002

- Overall NIV use was markedly increased.
  - 1st line NIV in preICU & ICU, postextubation NIV
  - Stable in acute-on-chronic RF, increase in cardiogenic PE
  - Decrease in de novo ARF

Intensive Care Med (2016) 42:82–92 DOI 10.1007/s00134-015-4087-4

Results

Univariate analysis: factors associated with failure of noninvasive ventilation for first-line episodes (n = 852)

		NIV failure (n = 316)	**NIV success** (n = 536)	P value
Chronic respiratory disease, n (%)		**159 (50)**	**345 (64)**	**0.002**
Cause of ARF	Acute-on-chronic ARF, n (%)	116 (37)	323 (60)	<0.0001
	Acute cardiogenic PE, n (%)	46 (15)	76 (14)	0.87
De novo ARF, n (%)		**152 (48)**	**134 (25)**	**<0.0001**
NIV episode				
SAPS II, At ICU admission		42 (33–54)	32 (26–40)	<0.0001
ABG prior to NIV	PaO_2/FiO_2 (mmHg)	194 (132–256)	226 (177–280)	0.0001
	$PaCO_2$ (mmHg)	47 (35–70)	56 (41–72)	0.0001
At NIV start				
Good NIV tolerance, n (%)		219 (69)	454 (85)	<0.0001
High level of leaks, n (%)		33 (56)	25 (42)	<0.0001
ABG prior to NIV	PaO_2/FiO_2 (mmHg)	171 (117–235)	237 (185–297)	<0.0001
	$PaCO_2$ (mmHg)	47 (35–68)	55 (43–69)	0.026
Duration of NIV (days)		2 (1–4)	3 (3–5)	<0.0001

- NIV success rate: up to 70 %
- Lowest NIV success rate in de novo ARF but not associated with increased mortality

Intensive Care Med (2016) 42:82–92 DOI 10.1007/s00134-015-4087-4

Summary

- Increase in the overall use of NIV as well as changes in NIV indication
  - Increased pre-ICU and post-extubation NIV
- NIV success rates increased over time
  - Technically advances and better patient selection
  - Highest failure rates in patients with de novo ARF

NIV should be used with discernment and the need for invasive MV promptly recognized in in de novo ARF.

Intensive Care Med (2016) 42:82–92 DOI 10.1007/s00134-015-4087-4

Ten Recent Advances That Could Not Have Come About Without Applying Physiology

Ten advances needing physiology

Assessment of fluid responsiveness
Estimating CO and left ventricular SV from arterial pressure
Choice of fluids for resuscitation
Dialysis and ultrafiltration may cause hypotension but for PP different reasons
P_{plat} and VT limits to minimize lung injury
Prone positioning to minimize lung injury and maximize gas exchange
Limiting airway pressure to optimize cardiovascular function
Optimizing PEEP according to the severity of lung injury
Extracorporeal gas exchange may be the future
Small changes in renal function may indicate significant kidney injury

Intensive Care Med (2016) 42:258–260 DOI 10.1007/s00134-015-3746-9