JOHNS HOPKINS
MEDICINE

Critical Illness Polyneuropathy and Myopathy:

Epidemiology and Risk Factors

Pedro A. Mendez-Tellez, MD

Johns Hopkins University
Baltimore, Maryland, USA

pmendez@jhmi.edu

Conflict of Interest

- I have no real or perceived conflict of interest that relates to this presentation.
- Any use of brand names is not in any way meant to be an endorsement of a specific product, but to merely illustrate a point of emphasis.

INTRODUCTION

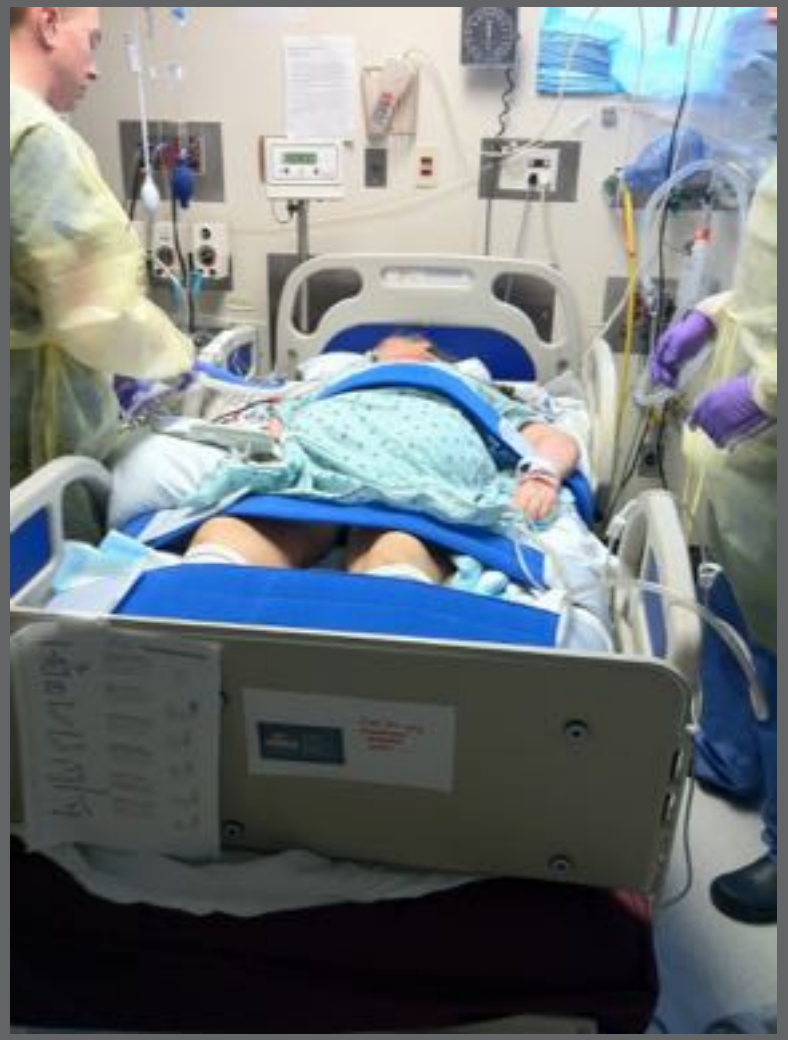
Introduction

- “In adults the disease may attack persons in good health, but who are overworked or ‘run down’ from any cause.
- Hemorrhage initiates the attack in a few cases.
- There may be repeated chills; the temperature is high, the pulse rapid, and the respirations are increased.
- The loss of flesh and strength is very striking.”

Sir William Osler, 1892
First Physician-in-Chief, JHH

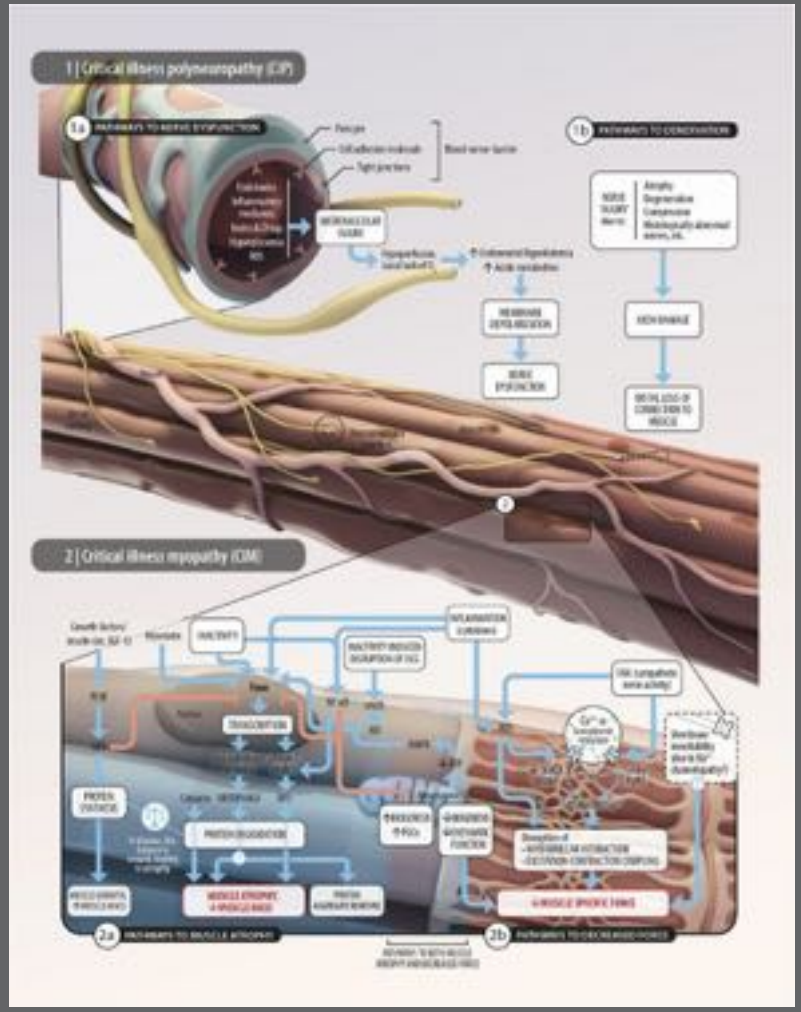
ICU-Acquired Weakness

- Generalized muscle weakness
- Develops during the ICU admission
- No other cause - besides “acute illness or its treatment”



ICU-Acquired Weakness can affect

- Peripheral nerves: “Critical Illness Polyneuropathy, (CIP)”,
- Skeletal muscle: “Critical Illness Myopathy, CIM”, or
- Both: “Critical Illness PolyNeuroMyopathy, CIPNM”.



ICU-Acquired Weakness

- Primary cause of muscle weakness and paralysis during and after critical illness.
- Appears to be triggered by the critical illness and ICU course, regardless of the underlying primary condition.
- The chances of developing weakness correlates with severity of illness.
- It cannot be explained by immobilization alone.

HISTORY, TIME COURSE AND CLINICAL FEATURES OF ICU-RELATED WEAKNESS

Differential diagnosis of acquired weakness

M	Medications: steroids, neuromuscular blockers (e.g., pancuronium or vecuronium), zidovudine, amiodarone
U	Undiagnosed neuromuscular disorder: myasthenia, Lambert–Eaton myasthenic syndrome, inflammatory myopathies, mitochondrial myopathy, acid maltase deficiency
S	Spinal cord disease: ischemia, compression, trauma, vasculitis, demyelination
C	Critical illness myopathy, critical illness polyneuropathy
L	Loss of muscle mass: cachectic myopathy, rhabdomyolysis
E	Electrolyte disorders: hypokalemia, hypophosphatemia, hypermagnesemia
S	Systemic illness: porphyria, AIDS, vasculitis, paraneoplastic syndromes, toxic disorders

*Maramattom, BV, Wijdicks, EF. Acute neuromuscular weakness in the intensive care unit. *Crit. Care Med.* 2006 **34**, 2835

Clinical characteristics of CIP and CIM

Critical illness polyneuropathy	Critical illness myopathy
Flaccid, symmetrical atrophy, and weakness of the limbs	Flaccid, symmetrical atrophy and weakness of the limbs and neck flexors
Distal>proximal	Proximal>distal
Lower limbs>upper limbs	
Facial muscles mostly spared	Facial muscles mostly spared
Deep tendon reflexes mostly reduced to absent but may be preserved	Deep tendon reflexes mostly reduced to absent but may be preserved
Variable distal sensory loss to pain, temperature, and vibration	No sensory loss
Weaning failure	Weaning failure

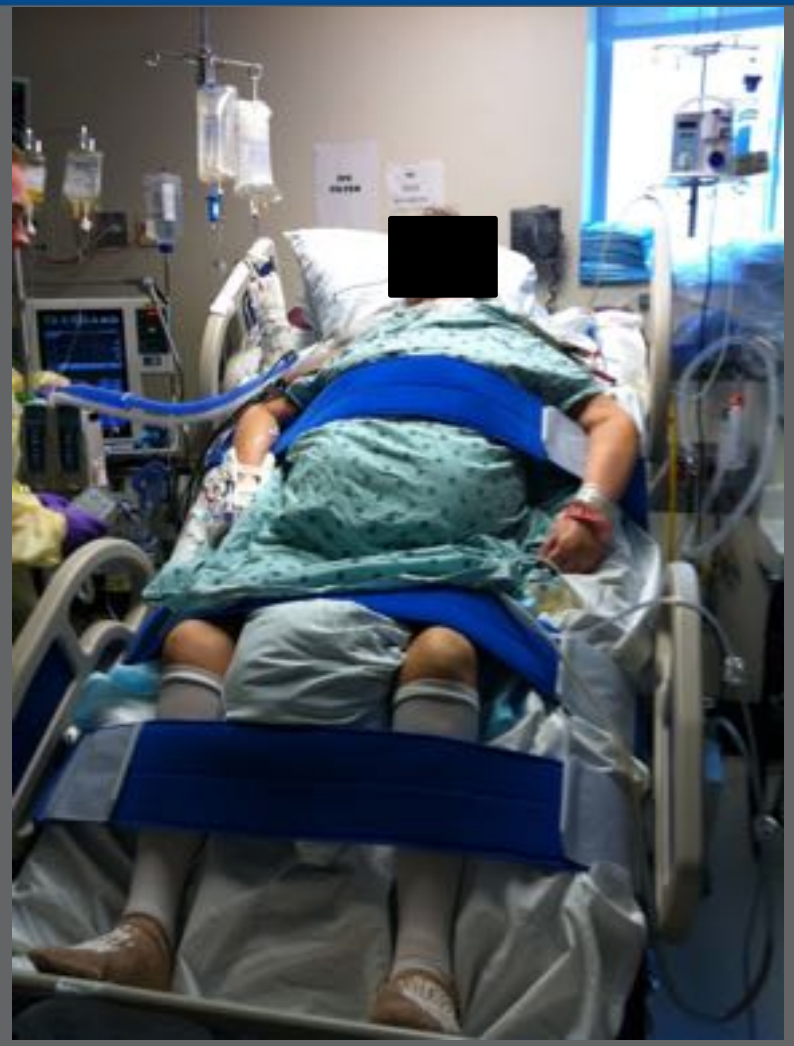
Spectrum of histological findings

Critical illness polyneuropathy	Critical illness myopathy
Nerve:	**Muscle:**
• Normal	• Focal or diffuse loss of thick myosin filaments
• Mildly reduced myelin fiber density with sporadic axonal degeneration	• Scattered to more prominent myonecrosis, vacuolization, and phagocytosis of muscle fibers
• Marked fiber loss with abundant degenerative changes	• Fiber atrophy with abnormal variation in size of muscle fibers, angulated fibers, fatty degeneration, fibrosis; mostly affecting both fiber types, may be limited to type II fibers
• Variable fiber regeneration	
Muscle:	**Nerve:**
• Denervation atrophy	• Normal

PREVALENCE AND RISK FACTORS

The actual incidence of ICUAW is difficult to ascertain...

- Reported rates strongly depend on the specific ICU subpopulations
- what risk factors these populations were exposed to,
- Diagnostic criteria used, and
- the timing of diagnosis during the acute illness.



Intensive Care Med (1998) 24: 1242–1250

REVIEW

B. De Jonghe
D. Cook
T. Sharshar
J.-P. Lefaucheur

Acquired neuromuscular disorders in critically ill patients: a systematic review

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

SYSTEMATIC REVIEW

Robert D. Stevens
David W. Dowdy
Robert K. Michaels
Pedro A. Mendez-Tellez
Peter J. Pronovost
Dale M. Needham

Neuromuscular dysfunction acquired in critical illness: a systematic review

Journal of the Intensive Care Society
2015, Vol. 16(2) 126–136

DOI: 10.1177/1751143714563016
jics.sagepub.com
SAGE

The incidence of intensive care unit-acquired weakness syndromes: A systematic review

Richard TD Appleton[1], John Kinsella[2] and Tara Quasim[2]

ICUAW Incidence – Summary of systematic reviews

Reference	Yr.	No. Studies	No. Patients	No. with ICUAW	Proportion with ICUAW (%)	95%CI
De Jonghe	1998	8	242	145	60	NR
Stevens	2007	24	1421	655	46	43-49
Appleton	2015	33	2686	1080	40	38-42

Prevalence and risk factors

Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

SYSTEMATIC REVIEW

Robert D. Stevens
David W. Dowdy
Robert K. Michaels
Pedro A. Mendez-Tellez
Peter J. Pronovost
Dale M. Needham

Neuromuscular dysfunction acquired in critical illness: a systematic review

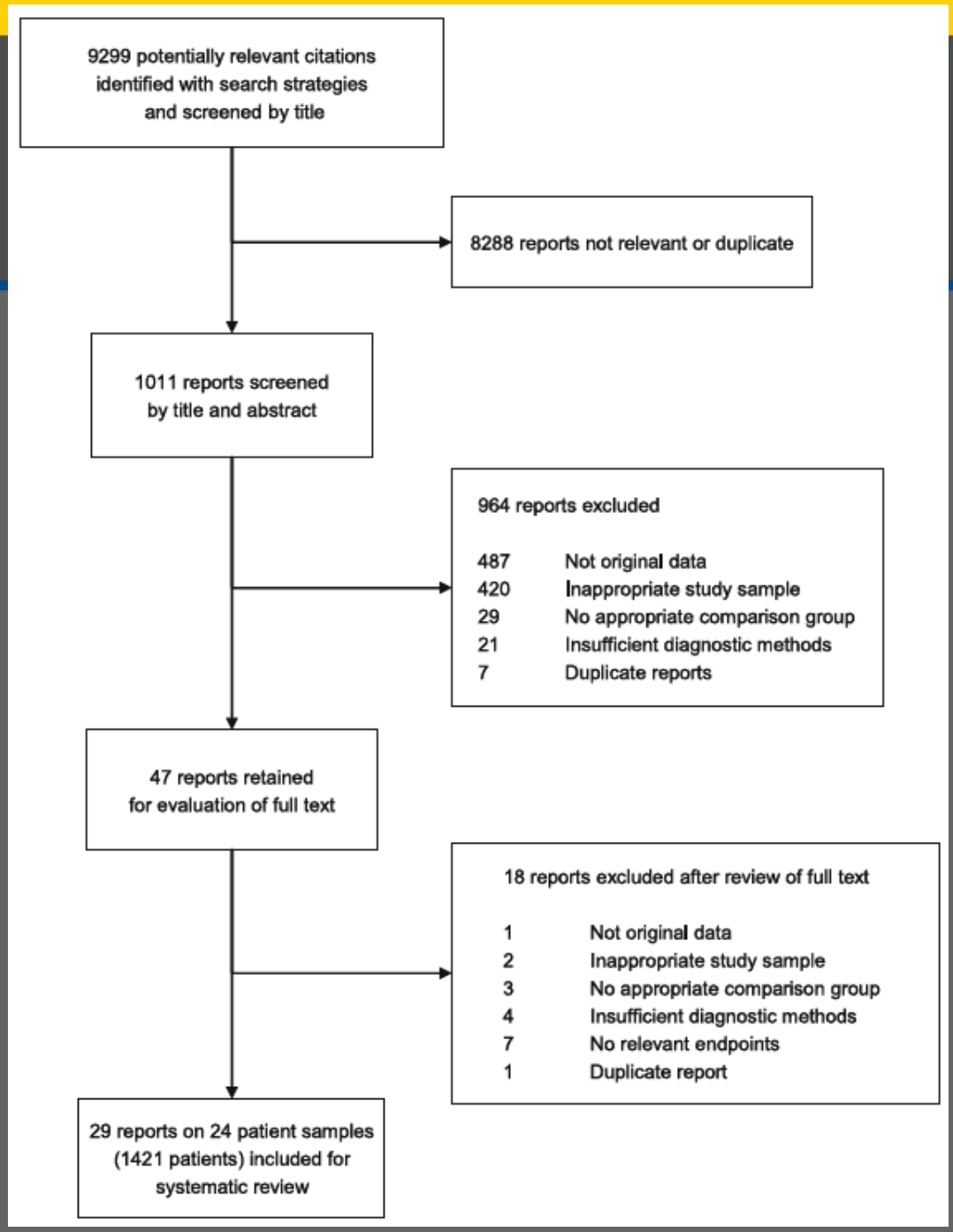
Intensive Care Med (2007) 33:1876–1891
DOI 10.1007/s00134-007-0772-2

SYSTEMATIC REVIEW

Robert D. Stevens
David W. Dowdy
Robert K. Michaels
Pedro A. Mendez-Tellez
Peter J. Pronovost
Dale M. Needham

Neuromuscular dysfunction acquired in critical illness: a systematic review

- Estimate the prevalence of ICUAW and its subsets using explicit diagnostic criteria
- Identify variables associated with (increased or decreased) risk for ICUAW
- Evaluate the relationship between ICUAW and patient outcomes



Reference	Study design	No. of patients enrolled	ICU Setting
Amaya-Villar, 2005 [24]	Prospective cohort	26	Mixed
Bednarik, 2003 [8]	Prospective cohort	46	Mixed (1 unit); Neurological (1 unit)
Bednarik, 2005 [22]	Prospective cohort	61	Mixed (1 unit); Neurological (1 unit)
Bercker, 2005 [48]	Retrospective cohort	45	Mixed
Berek, 1996 [34]	Prospective cohort	22	Not reported
Campellone, 1998 [35]	Prospective cohort	77	Surgical
Coakley, 1998 [36]	Prospective cohort	44	Mixed
De Jonghe, 2002 [7]	Prospective cohort	95	Medical (3 units); Surgical (2 units)
De Letter, 2001 [52]	Prospective cohort	98	NR
Druschky, 2001 [38]	Prospective cohort	28	Neurological
Garnacho-Montero, 2001 [25]	Prospective cohort	73	Mixed
Garnacho-Montero, 2005 [51]	Prospective cohort	64	Mixed
Hund, 1997 [50]	Prospective cohort	28	Surgical
Kupfer, 1992 [40]	Prospective cohort	10	Medical
Lefaucheur, 2006 [41]	Prospective cohort	30	Medical
Leijten, 1995 [43]	Prospective cohort	50	Mixed
Leijten, 1996 [42]	Prospective cohort	38	Mixed
Mohr, 1997 [44]	Prospective cohort	33	Mixed
Rudis, 1996 [49]	Case–control study	20	Mixed
Tepper, 2000 [45]	Prospective cohort	22	Mixed
Thiele, 1997 [50]	Case–control study	44	Surgical
Thiele, 2000 [46]	Prospective cohort	19	Surgical
Van den Berghe, 2005 [54]	Randomized controlled trial	405	Mixed (mostly cardiac surgical)
Witt, 1991 [47]	Retrospective cohort	43	Mixed

JOHNS HOPKINS MEDICINE

Stevens RD, et al. 2007

Reference	Patient enrollment criteria	Follow up
Amaya-Villar, 2005 [24]	MV > 48 h, COPD, high-dose steroids	In-hospital only
Bednarik, 2003 [8]	> 2 organ failures with SOFA grade 3–5	28 days after enrollment
Bednarik, 2005 [22]	> 2 organ failures with SOFA grade 3–5	28 days after enrollment
Bercker, 2005 [48]	ARDS and MV	29 days after enrollment
Berek, 1996 [34]	SIRS or sepsis and MOF	60–90 days after enrollment
Campellone, 1998 [35]	MV > 7 days or hospital LOS > 14 days following OLT	NR
Coakley, 1998 [36]	MV and ICULOS > 7 days	In-hospital only
De Jonghe, 2002 [7]	MV > 7 days and evidence of wakefulness	45 days after enrollment
De Letter, 2001 [52]	MV > 3 days	30 days after intubation
Druschky, 2001 [38]	MV > 4 days	14 days of MV
Garnacho-Montero, 2001 [25]	MV > 10 days, sepsis, MOF	In-hospital only
Garnacho-Montero, 2005 [51]	MV > 7 days, severe sepsis or septic shock	In-hospital only
Hund, 1997 [50]	"Prolonged" MV, sepsis	ICU only
Kupfer, 1992 [40]	MV, vecuronium infusion	ICU only
Lefaucheur, 2006 [41]	MV > 7 days, diffuse weakness	NR
Leijten, 1995 [43]	MV > 7 days, age < 75	12 months
Leijten, 1996 [42]	MV > 7 days, age < 76	12 months
Mohr, 1997 [44]	MOF (Goris score > 5 for > 5 days)	In-hospital only
Rudis, 1996 [49]	Cases: weakness after NMB	In-hospital only
Tepper, 2000 [45]	Septic shock	ICU only
Thiele, 1997 [50]	MV > 3 days, cardiac surgery	ICU only
Thiele, 2000 [46]	MV > 3 days, cardiac surgery	ICU only
Van den Berghe, 2005 [54]	MV, EMG in subset with ICU LOS ICU LOS > or = 7 days	In-hospital only
Witt, 1991 [47]	ICU LOS > 5 days, sepsis	6 months

Reference	No. of patients enrolled	No. (%) with CINMA
Amaya-Villar, 2005 [24]	26	9 (35%)
Bednarik, 2003 [8]	46	26 (57%)
Bednarik, 2005 [22]	61	35 (57%)
Bercker, 2005 [48]	45	27 (60%)
Berek, 1996 [34]	22	18 (82%)
Campellone, 1998 [35]	77	7 (9%)
Coakley, 1998 [36]	44	37 (84%)
De Jonghe, 2002 [7]	95	24 (25%)
De Letter, 2001 [52]	98	32 (33%)
Druschky, 2001 [38]	28	16 (57%)
Garnacho-Montero, 2001 [25]	73	50 (68%)
Garnacho-Montero, 2005 [51]	64	34 (53%)
Hund, 1997 [50]	28	20 (71%)
Kupfer, 1992 [40]	10	7 (70%)
Lefaucheur, 2006 [41]	30	26 (87%)
Leijten, 1995 [43]	50	29 (58%)
Leijten, 1996 [42]	38	18 (47%)
Mohr, 1997 [44]	33	7 (21%)
Rudis, 1996 [49]	20	10 (50%)
Tepper, 2000 [45]	22	19 (86%)
Thiele, 1997 [50]	44	7 (16%)
Thiele, 2000 [46]	19	12 (63%)
Van den Berghe, 2005 [54]	405	155 (38%)
Witt, 1991 [47]	43	30 (70%)

Factors commonly associated with ICUAW

Severe sepsis and MODs

Neuro/Myotoxics:
- NMBAs
- Steroids

Prolonged mechanical ventilation

Bed rest / Immobilization

Malnutrition

Hyperglycemia
Insulin resistance

ICUAW was independently predicted by the following factors [OR/RR (95% CI)]

Female gender	OR 4.6 (1.2–18.3)
Renal replacement therapy	OR 1.9 (1.0– 3.8)
APACHE III score 30 days after starting of MV	OR 5.2 (2.8– 9.8)
SOFA score 1 week after ICU admission	RR 2.4 (1.02–5.53)
SIRS 1 week after admission	RR 3.74 (1.37–10.20)
SIRS 30 days after starting of MV	OR 2.5 (1.2–4.8)
blood glucose levels	OR 1.24 (1.14–1.36) per 20 mg/dl increment
Total parenteral nutrition	OR=5.1 (1.1–23.0)

ICUAW - Pharmacologic Risk factors (OR (95% CI)

Multivariable analysis suggested a relationship between ICUAW and:

- Corticosteroids in 1 of 2 studies [OR = 14.9 (3.2–69.8)]
- NMBAs in 1 out of 3 studies [OR =16.32 (1.34–199)].

LONG-TERM PHYSICAL IMPAIRMENTS IN ARDS SURVIVORS

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 20, 2003 VOL. 348 NO. 8

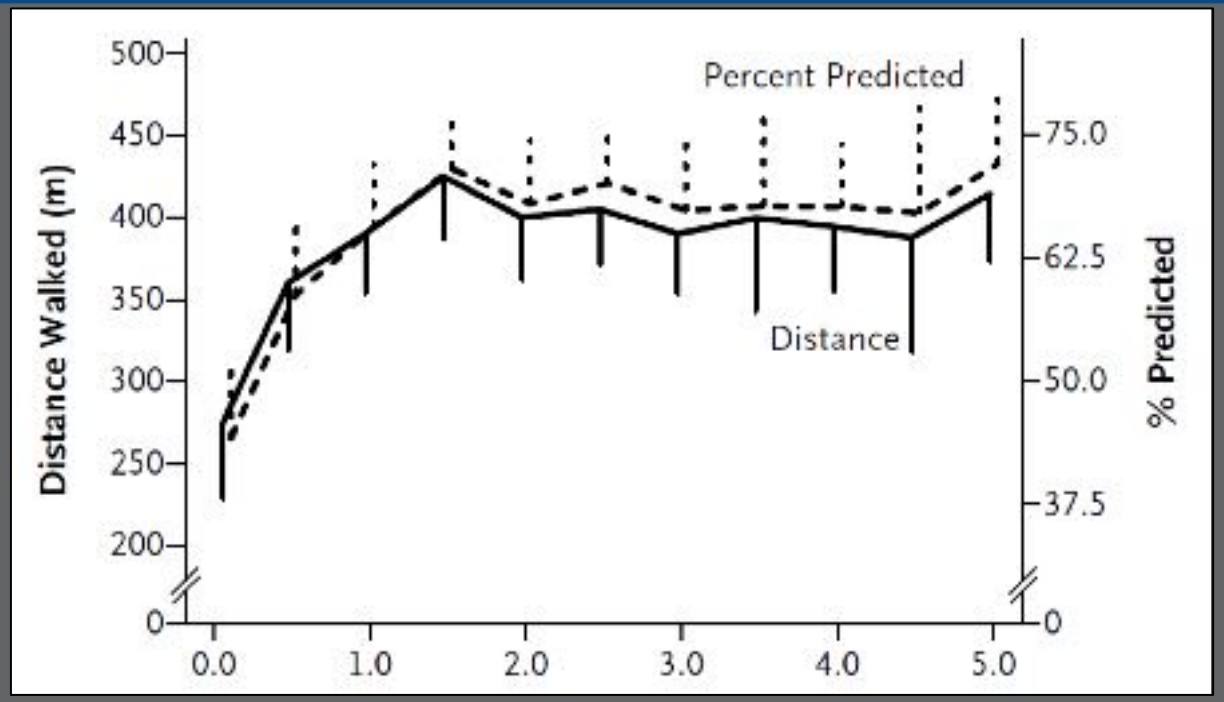
One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome

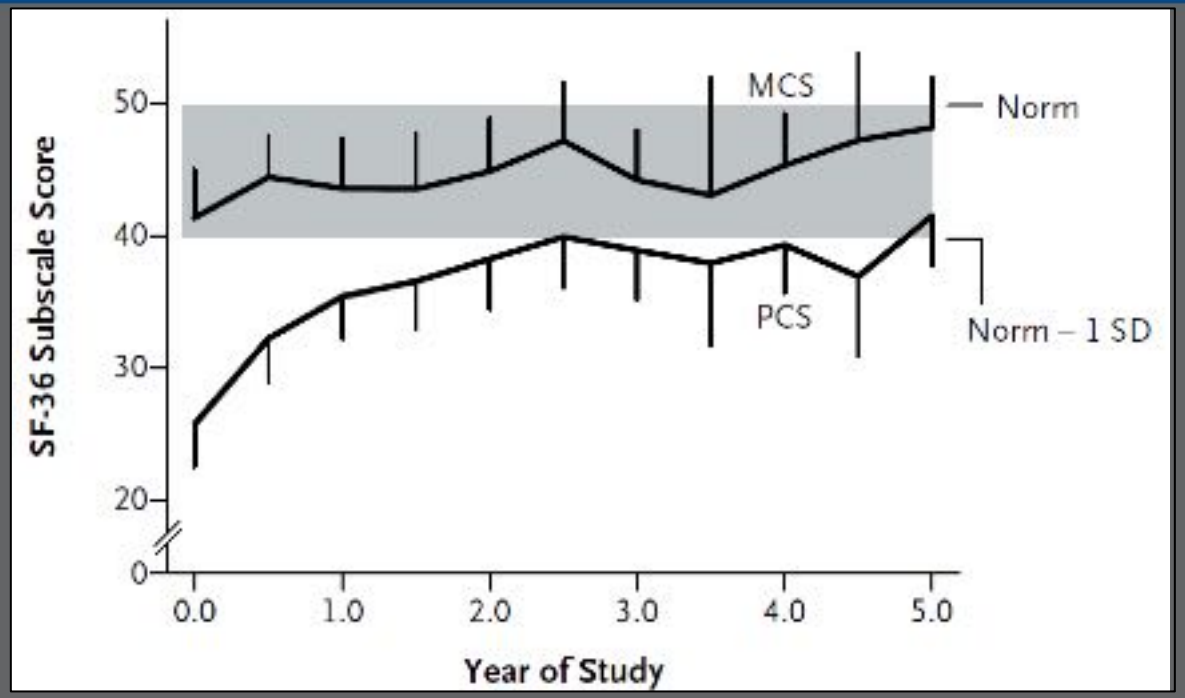
Margaret S. Herridge, M.D., M.P.H., Angela M. Cheung, M.D., Ph.D., Catherine M. Tansey, M.Sc., Andrea Matte-Martyn, B.Sc., Natalia Diaz-Granados, B.Sc., Fatma Al-Saidi, M.D., Andrew B. Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Aiala Barr, Ph.D., Deborah Cook, M.D., and Arthur S. Slutsky, M.D., for the Canadian Critical Care Trials Group

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

Long-term functional disability in ARDS survivors





6-MDW	3-Mo (n=80)	6-Mo (n=78)	1-yr (n=81)	2-yr (n=69)	3-yr (n=71)	4-yr (n=63)	5-yr (n=64)
% predicted	49%	64%	66%	68%	67%	71%	76%

- ARDS survivors report substantial impairment in physical function and HR-QOL functional status up to 5 years after ICU discharge
- Unknown whether physical impairments correlate longitudinally with objective measures of muscle strength.

Recovery from ICUAW

JOHNS HOPKINS MEDICINE

Physical Complications in Acute Lung Injury Survivors: A 2-Year Longitudinal Prospective Study

Eddy Fan, MD, PhD[1,2]; David W. Dowdy, MD, PhD[2,3]; Elizabeth Colantuoni, PhD[2,4]; Pedro A. Mendez-Tellez, MD[2,5]; Jonathan E. Sevransky, MD, MHS[6]; Carl Shanholtz, MD[7]; Cheryl R. Dennison Himmelfarb, RN, PhD[8]; Sanjay V. Desai, MD[2,9]; Nancy Ciesla, DPT[2]; Margaret S. Herridge, MD, MPH[1]; Peter J. Pronovost, MD, PhD[2,5,8,10]; Dale M. Needham, MD, PhD[2,9,11]

Crit Care Med 2014. 42: 849

Risk Factors for Physical Impairment after Acute Lung Injury in a National, Multicenter Study

Dale M. Needham[1,2,3], Amy W. Wozniak[1,4], Catherine L. Hough[5], Peter E. Morris[6], Victor D. Dinglas[1,2], James C. Jackson[7], Pedro A. Mendez-Tellez[1,8], Carl Shanholtz[9], E. Wesley Ely[7,10], Elizabeth Colantuoni[1,4], and Ramona O. Hopkins[11,12]; with the National Institutes of Health NHLBI ARDS Network*

Am J Respir Crit Care Med 2014. 189: 1214

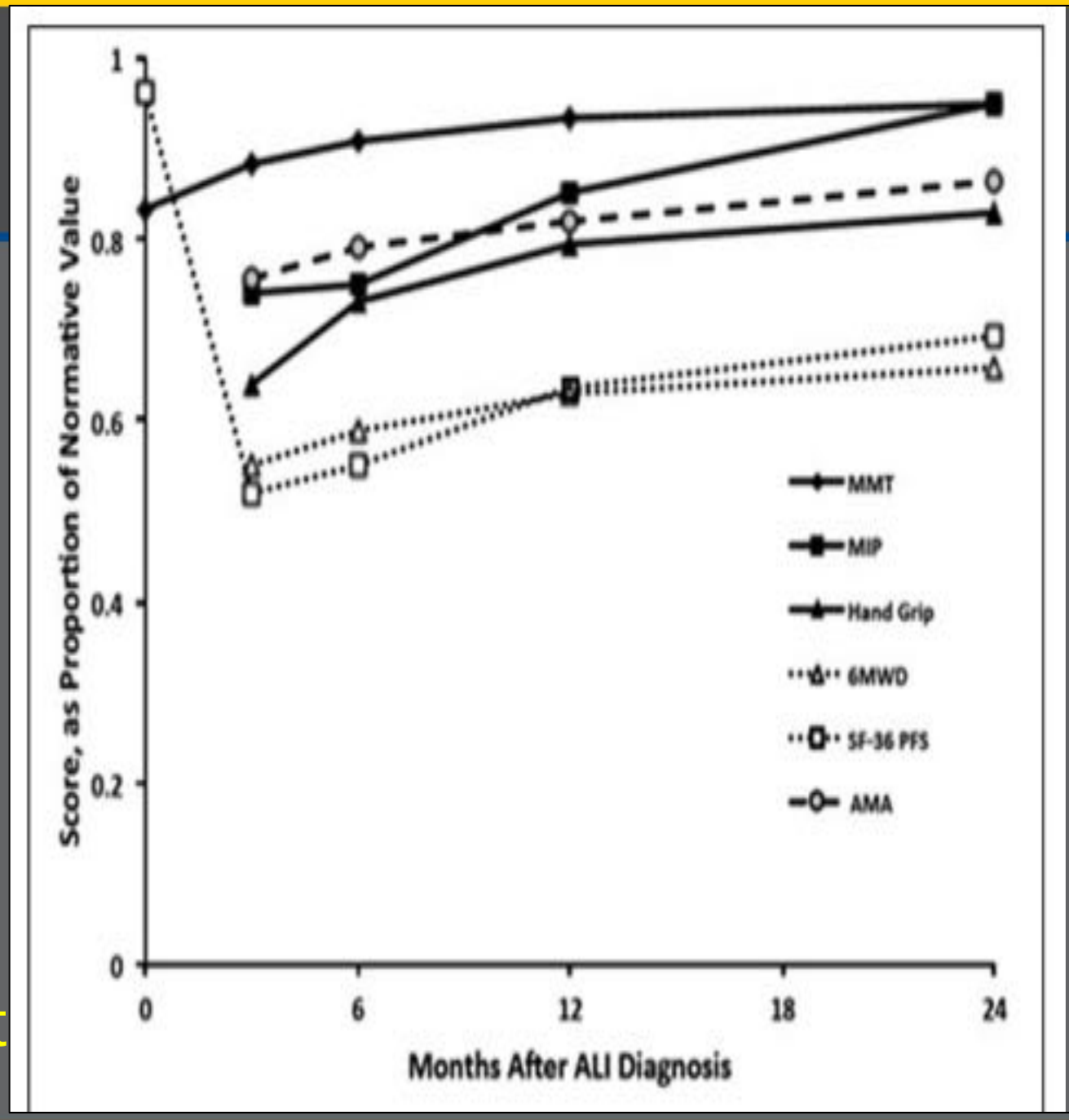
The ICAP study: Physical impairments in ARDS survivors at 2 years

- To determine the longitudinal epidemiology of muscle weakness, physical function and HR-quality of life.
- Muscle strength Measures
  - Extremity, respiratory (MMT/MRC score and Handgrip dynamometry, MIP)
- Anthropometrics
  - Wt, BMI, mid-arm circumference, triceps skinfold thickness
- 6MWD
- HR-QOL: SF-36 Physical Function Score (PFS)

- Proportion of ICUAW:
  - 36% at hospital discharge
  - 22% at 3 months
  - 15% at 6 Mo.
  - 14% at 12 Mo.
  - 9% at 2 yrs

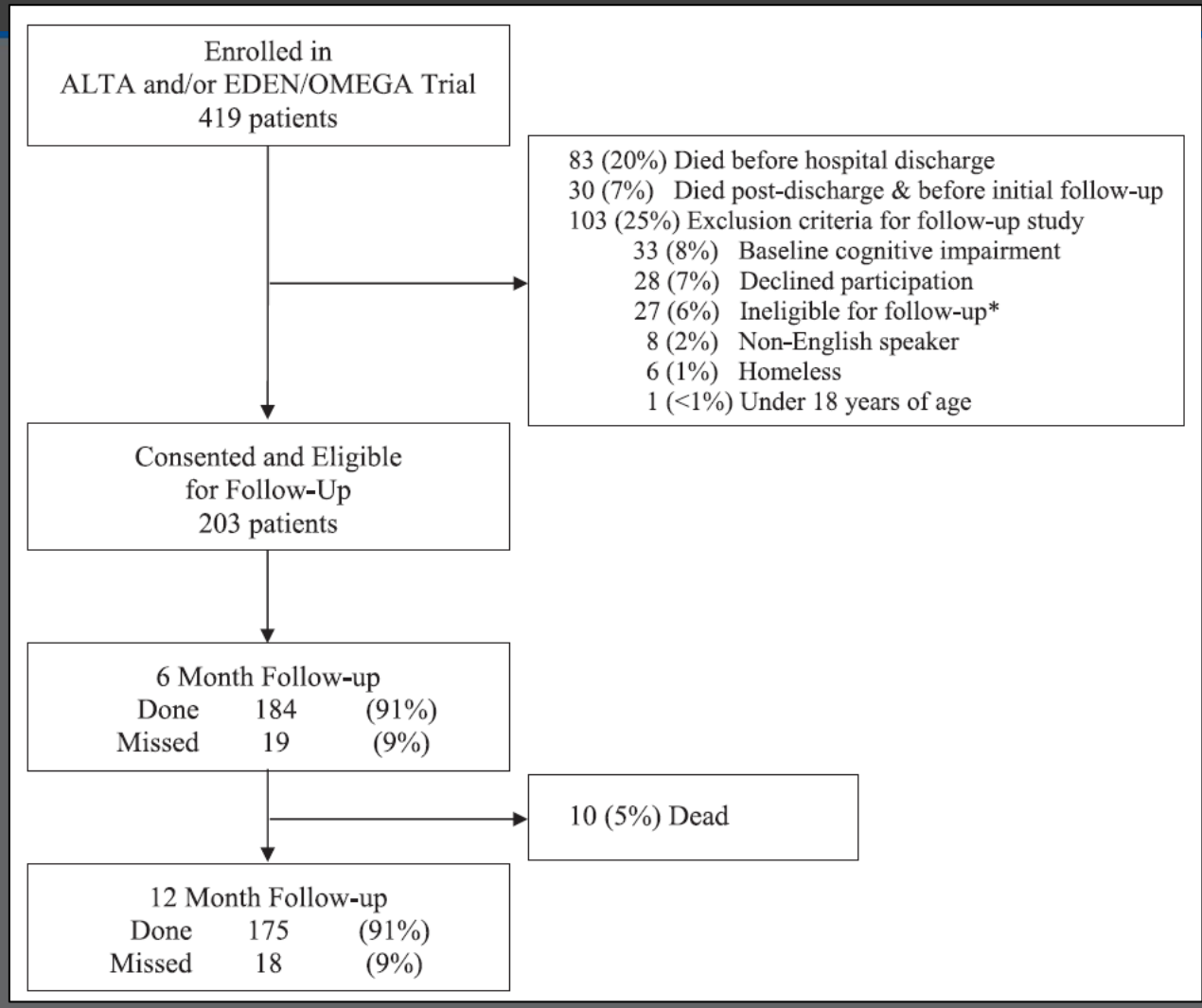
- 6MWD and SF36-PFS substantially impaired (52-69% predicted)

- No association with CS / NMBAs
- Positive association with bed rest



The ARDSNet Long-Term Outcomes Study (ALTOS). Needham DM.

- To evaluate risk factors for physical impairment in ARDS survivors
- Prospective longitudinal study of physical outcomes at 6-12 Mo.
  - Muscle strength
  - 6 min. walk distance
  - SF-36 Physical function score
- 203 ARDS survivors



Physical Outcome	Strength (% of Maximum MMT Score) (n = 191)*	6-Minute-Walk Test (% Predicted) (n = 183)*	SF-36 Physical Function (% Predicted) (n = 200)*
6-month, mean (SD)	92 (8)†	64 (22)‡	61 (36)
12-month, mean (SD)	93 (9)†	67 (26)‡	67 (37)

At 6 Mo.:

- 13 / 169 (8%) of ARDS survivors had ICUAW
- The mean % predicted value for 6MWD was 64.
- The mean % predicted value for SF36-PCS was 61.

At 12 Mo.: Small improvement in ALL physical outcome measures

Significant association btwn Corticosteroids and ICU LOS and physical function impairments

Conclusions

- ICUAW is a common complications of critical illness (~40%)
- Incidence is higher in patients with severe sepsis.
- The longer the exposure to MV, the higher the incidence.
- Other factors associated with ICUAW include: prolonged bed rest, hyperglycemia, MODS, and neuro/myotoxic agents.
- Minimizing steroid dose and reducing patient immobilization may impact ICU survivors' physical outcomes.

Conclusions

- In ARDS survivors, ICUAW is common and is associated with substantial physical impairments.
- In these subgroup, muscle weakness resolves within 1 year.

JOHNS HOPKINS
MEDICINE

THANK YOU

Questions ?

Contact Information

Pedro Mendez-Tellez, MD
Johns Hopkins University
pmendez@jhmi.edu