La medicina americana: un’utile esperienza

Morandi A

*Riabilitazione Ancelle della Carità, Cremona*
*Gruppo di Ricerca Geriatrica*

11 Novembre 2011, Brescia
La ricerca nella medicina americana (1): 2007-2011
La ricerca nella medicina americana (2)

Vanderbilt Center for Quality Aging

Documentation and Management of Words Associated With Delirium Among Elderly Patients in Postacute Care: A Pilot Investigation

Alessandro Morandi, MD, Laurence M. Solberg, MD, Ralf Habermann, MD, Patrick Cleeton, Emily Peterson, E. Wesley Ely, MD, MPH, and John Schnelle, PhD

JAMDA 2009

Older ICU Survivors and Inappropriate Medications: Types and Risk Factors

Under review JHospMed

Less Is More

Inappropriate Medications in Elderly ICU Survivors: Where to Intervene?

Alessandro Morandi, MD
Eduard E. Vasilevskis, MD
Pratik P. Pandharipande, MD, MSCI
Timothy D. Girard, MD, MSCI
Laurence M. Solberg, MD
Erin B. Neal, PharmD
Tyler Koestner, MS
Renee Torres, MS
Jennifer L. Thompson, MPH
Ayumi K. Shintani, PhD, MPH
Jin H. Han, MD, MSc
John Schnelle, PhD
Donna M. Fick, PhD
E. Wesley Ely, MD, MPH
Sunil Kripalani, MD, MSc

ARCH INTERN MED/VOL 171 (NO. 11), JUNE 13, 2011
Effect of Preinjury Statin Use on Mortality and Septic Shock in Elderly Burn Patients

Mary D. Fogerty, MD, MPH, David Efron, MD, Alessandro Morandi, MD, Jeffrey S. Guy, MD, Naji N. Abumrad, MD, and Adrian Barbul, MD

The Journal of TRAUMA® Injury, Infection, and Critical Care • Volume 69, Number 1, July 2010

Feasibility, efficacy and safety of Rosuvastatin in reducing inflammation in Burn Patients: A Randomized Double-Blind Placebo Controlled Trial


Under submission
La ricerca nella medicina americana (4)

Intensive Care Unit (ICU) delirium

Emergency Department (ED) delirium
ED Delirium

Delirium in the Nursing Home Patients Seen in the Emergency Department  JAGS  57:889–894, 2009

Jin H. Han, MD, MSc, * Alessandro Morandi, MD, †‡ E. Wesley Ely, MD, MPH, †§‖ Clay Callison, MD, #
Chuan Zhou, PhD, *∗ Alan B. Storrow, MD, *, Robert S. Dittus, MD, MPH, †‖ †† Ralf Habermann, MD, ††
and John Schnelle, PhD ††

Delirium in Older Emergency Department Patients: Recognition, Risk Factors, and Psychomotor Subtypes

Jin H. Han, MD, MSc, Eli E. Zimmerman, BA, Nathan Cutler, John Schnelle, PhD, Alessandro Morandi, MD, Robert S. Dittus, MD, MPH, Alan B. Storrow, MD, and E. Wesley Ely, MD, MPH

ACADEMIC EMERGENCY MEDICINE 2009; 16:1–8

Delirium in Older Emergency Department Patients Is an Independent Predictor of Hospital Length of Stay

Jin H. Han, MD, MSc, Svetlana Eden, MS, Ayumi Shintani, MPH, PhD, Alessandro Morandi, MD, John Schnelle, PhD, Robert S. Dittus, MD, MPH, Alan B. Storrow, MD, and E. Wesley Ely, MD, MPH

ACADEMIC EMERGENCY MEDICINE 2011: 18:1–7

Delirium in the Emergency Department: An Independent Predictor of Death Within 6 Months

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Ayumi Shintani, MPH, PhD
Svetlana Eden, MS
Alessandro Morandi, MD
Laurence M. Solberg, MD
John Schnelle, PhD
Robert S. Dittus, MD, MPH
Alan B. Storrow, MD
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From the Department of Emergency Medicine (Han, Storrow), the Department of Biostatistics (Shintani, Eden), and the Department of Internal Medicine, Division of Allergy, Pulmonary, and Critical Care (Morandi, Ely) and Division of General Internal Medicine (Solberg, Schnelle, Dittus), Vanderbilt University Medical Center, Nashville, TN; and the Veterans Affairs Tennessee Valley Geriatric Research, Education and Clinical Center, VA Service, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System, Nashville, TN (Solberg, Dittus, Ely).

Ann Emerg Med. 2010
ICU Delirium

- Epidemiologia
- Patogenesi
- Diagnosi
- Trattamento e prevenzione
- Outcomes
Prevalence: ICU Delirium

- Up to 80% ICU ventilated patients develop delirium
- Between 20-50% of lower severity ICU patients develop delirium

Ely EW, ICM, 2001;27:1892-1900
Ely EW, JAMA, 2001;286,2703-2710
Pandharipande P, J Trauma, 2008;65:34-41
Ely EW, CCM, 2001;29:1370-1379
Pandharipande P, ICM, 2007;33:1726-1731
Lat I, CCM, 2009;37:1898-1905

Roberts B, Aust Crit Care, 2005;18:6,8-9
Thomason J, Crit Care, 2005;9:375-381
Ely EW, CCM, 2004;32:106-112
Peterson, JAGS, 2006;54:479-484
Ouimet S, ICM, 2007;33:66-73
Slooter A, CCM, 2009;3:1881-1885
Outcomes: ICU Delirium

- $15k to $25k higher hospital costs
- Longer hospital stays
- 3 times higher risk of death by 6 months
- 10% higher risk of death by 1 year per day of delirium
- Prolonged neuropsychological dysfunction

ICU Delirium and Cognitive Performance

$P = .005$

Cognitive Function at 12 Months (Predicted Mean T-score)

Days of ICU Delirium

Girard TD, et al. CCM;38:1513-20
ICU Delirium

- Epidemiologia
- Patogenesi
  - Diagnosi
  - Outcomes
Bringing to light Risk factors And Incidence of Neuropsychological dysfunction in ICU survivors
The BRAIN ICU Project
- Overview -

INDEPENDENT VARIABLES

Patient enrollment

Time

Drug Exposure
Delirium Duration

12-month follow-up

DEPENDENT VARIABLES

Long Term Cognitive Impairment (LTCl) Battery
Health-Related Quality of Life (HRQL) Battery
Pathogenesis of Delirium: Different Hypotheses and Mechanisms

- Neuroinflammation
- Neurotransmitters-Amino Acid perturbation
- Limbic-hypothalamic-pituitary-adrenal axis
- Reduced cerebral perfusion and metabolism
- Direct exposures to sedatives and analgesics

Maldonado JR, Critical Care Clin 2008;24:789-756
MacLullich AM, J Psychosom Res. 2008;65:229-38
Cerejeira J, Acta Neuropathol 2010;119:737-54
Simmone MJ, CNS Neurosc Ther 2010 Epub
Neuroinflammation and Delirium

Cerejeira J, Acta Neuropahol 2010;119:737-54
Association of inflammation with the cholinergic pathway

Cytokines, Acetylcholine, & Delirium

Systemic infection

TNFα

Activated microglia

Cholinergic Inhibition of microglial activation

Delirium

Cytokines, Acetylcholine, & Delirium

Old age, incipient neurodegenerative disease, or anticholinergics

Systemic infection

- TNFα

- Primed microglia

- Reduced cholinergic inhibition of microglia

- Overactivated microglia

- TNFα

Neurodegeneration

Severe, prolonged delirium

Dementia

Association of dopamine, norepinephrine, and serotonin with the cholinergic pathway

Neurotransmitters and Amino Acids
Precursors

- Phenylalanine
  - Tyrosine
  - Dopamine
  - Norepinephrine
  - Epinephrine

- Tryptophan
  - Serotonin
  - Melatonin
The Monoamine axis Hypothesis

• Serotonin, dopamine and norepinephrine may play an important role in the pathogenesis of delirium

• Bioavailability of amino acid precursors influence neurotransmitter synthesis by competing with the LAT-1 transporter in the blood brain barrier

  – Tryptophan $\rightarrow$ Serotonin
  – Tyrosine, Phenylalanine $\rightarrow$ Dopamine and Norepinephrine

Acute tryptophan depletion dose dependently impairs object memory in serotonin transporter knockout rats


Low Tryptophan Levels Are Associated with Post-Operative Delirium in the Elderly

Thomas N Robinson, MD¹, Christopher D Raeburn, MD¹, Erik M Angles, BS¹, and Marc Moss MD²


Plasma Trp and Tyr levels: Risk Factors for Delirium

- **Hypothesis**: association of Trp, Tyr, and Phe/LNAA ratios with transitioning to delirium in mechanically ventilated ICU patients

Plasma Tyr/LNAA Ratio and Risk of Delirium

- Phenylalanine
- Tyrosine
- Dopamine
- Norepinephrine
- Epinephrine

Plasma Trp/LNAA Ratio and Risk of Delirium

Amino acids and Delirium (2)

10-15%

Tryptophan

80-95%

Indoleamine-2-3 dioxygenase (IDO)

Kynurenine

5-hydroxytryptophan

5-hydroxytryptamine (serotonin)

Melatonin

Sleep regulation and somnolence

Kynurenine acid

Neuroprotective effects

3-hydroxykynurenine

3-hydroxyanthanilic acid

Quinolinic acid

Neurotoxic effects

Hypothesis: to determine if KYN levels and/or KYN/TRP ratio (KYN pathway activity) were associated with duration of acute brain dysfunction (delirium/coma-free days, DCFDs)
KYN Levels and Probability of DCFDs

KYN/TRP Ratio and Probability of DCFDs

Pathogenesis of Delirium: Different Hypotheses and Mechanisms

- Neuroinflammation and neuroprotection
- Neurotransmitters-Amino Acid perturbation
- Limbic-hypothalamic-pituitary-adrenal axis
- Reduced cerebral perfusion and metabolism
- Direct exposures to sedatives and analgesics

Maldonado JR, Critical Care Clin 2008;24:789-756
MacLullich AM, J Psychosom Res. 2008;65:229-38
Cerejeira J, Acta Neuropathol 2010;119:737-54
Simmone MJ, CNS Neurosc Ther 2010 Epub
Neuroprotection Hypotheses

- Innate neuroprotection: IGF-1
- Pharmacological neuroprotection: Statins
Insuline Like Growth Factor-1: Neuroprotective “cytokine”

- Neuroprotective actions: cortical, hippocampal, and dopaminergic neurons
- IGF-1 blocks apoptosis, promotes neural plasticity, neurogenesis
- *Low IGF-1 may increase neurons vulnerability and increase delirium*

Low levels of IGF1 were associated with incident and prevalent delirium in elderly non critically ill medical patients.

No association between IGF-1 levels and post-operative delirium.

Lemstra AW, et al. 2008 Int J Ger Psych; 23:943-948
Serum IGF-1 and Acute Brain Dysfunction in the ICU

• Hypothesis: Low levels of IGF-1 early during critical illness are associated with delirium risk and duration of brain dysfunction (delirium/coma-free days DCFDs)

IGF-1 and Risk of Delirium

IGF-1 and Duration of Acute Brain Dysfunction

Statine e Delirium
Severe sepsis incidence is as high as 750,000 cases a year of whom 383,000 (51%) are admitted to the ICU

Pathogenesis of Delirium

- \textit{Neuroinflammation (sepsis)}
- Neurotransmitters
- Aminoacid perturbation
- Multifactorial

Maldonado JR, Critical Care Clin 2008;24:789-756
Cerejeira J, Acta Neuropahol 2010;March 24
Angus DC, Crit Care Med 2001;29:1303-10
Statins and Prevention of Sepsis/Infectious Complications

Tleyjah I.M, Arch Int Med 2009;169:1658-1667
Statins and Brain Dysfunction

A Hypothesis to Reduce the Burden of Cognitive Impairment in Patients Who Are Critically Ill

Alessandro Morandi, MD, MPH; Christopher G. Hughes, MD; Timothy D. Girard, MD, MSCI; Danny F. McAuley, MD; E. Wesley Ely, MD, MPH, FCCP; and Pratik P. Pandharipande, MD, MSCI

Morandi A et al, Chest 2011;140:580-585
The systemic inflammatory cascade and delirium

Morandi A et al, Chest 2011;140:580-585
Statin effect on inflammation and delirium

Morandi A et al, Chest 2011;140:580-585
The microglia phenotypes, delirium, and action of statins in critical illness

Morandi A et al, Chest 2011;140:580-585
Clinical Data on Statins and Delirium

- Observational studies: inconsistent results on the effect of statins on postoperative delirium in cardiac surgery patients
- No data on the effect of statins on delirium risk in ICU patients

Redelmeier DA, CMAJ 2008;23:645-52
Effect of Statin Discontinuation

- IL-6 and CRP increased after discontinuation of statins (3 to 5 days)
- Increased risk of Subaracnoid haemorrhage (<30 days)
- 8-fold increase in risk of neurological deterioration (3 days)

Li J, Clin Chim Acta 2006;366:269-73
Sposito AC, Atherosclerosis 2009;207:191-4
Blanco M, Neurology 2007;69:904-910
Objectives of the Study

• To assess the association between statin use and the daily risk of delirium in the ICU in a cohort of 800 critically ill patients

• To assess the association between statin discontinuation and the daily risk of delirium

Morandi et al. Undergoing
**Pathogenesis of Delirium: Different Hypotheses and Mechanisms**

- Neuroinflammation
- Neurotransmitters-Amino Acid perturbation
- Limbic-hypothalamic-pituitary-adrenal axis
- **Reduced cerebral perfusion and metabolism**
- Direct exposures to sedatives and analgesics

Maldonado JR, Critical Care Clin 2008;24:789-756
MacLullich AM, *J Psychosom Res.* 2008;65:229-38

Simmone MJ, *CNS Neurosc Ther* 2010 Epub
Structural damage and delirium

Brain lesions (i.e. hemorrhage, hematoma, infarct) in elderly emergency room patients may contribute to delirium (CT), but results are inconsistent and future research is needed.

Brain perfusion and delirium (1)

• A SPECT study has identified frontal and parietal cerebral perfusion abnormalities
• Left inferior frontal, right temporal, right occipital and pons.

Brain perfusion and delirium (2)

- Hypoperfusion in the frontal, temporal, occipital cortex and thalamus and basal ganglia (Xenon-enhanced CT).

Yokota H, 2003 Psychiatry Clinic Neuroscience;61:1294-99
Brain areas and delirium

- Frontal and parietal;
- Left Dorso-Lateral Prefrontal Cortex;
- Left inferior frontal, right temporal, right occipital, pontine, thalamus and basal ganglia.
Features of delirium and brain areas

Attention:
- Nondominant posterior parietal
- Bifrontal areas
- Thalamus
- Pons

Orientation:
- Nondominant parietal
- Medial orbifrontal and temporal cortex

Comprehension:
Frontal and temporal regions

Trzepacz PT, 1999 Dement Geriatr Cogn Disord;10:330-34
Schnider A, 1996 Brain;119:1627-32
Ushijima Y, 2002 Nucl Med Commun;23:779-84
Delirious ARDS patient imaged 6 months following ICU care with 40 point drop in IQ and profound *de novo* cerebral atrophy.
The Association between Brain Volumes, Delirium Duration and Cognitive Outcomes in Intensive Care Unit Survivors: A Prospective Exploratory Cohort Magnetic Resonance Imaging Study

Max L. Gunther¹-⁵ PHD, Alessandro Morandi⁴-⁶ MD, MPH, Erin Krauskopf⁷ BS, Pratik Pandharipande⁸, ⁹ MD, MSCI, Timothy D. Girard⁴-⁶, ¹⁰ MD, MSCI, James C. Jackson¹, ⁴, ⁵, ¹⁰ PSYD, Jennifer Thompson¹¹ MPH, Ayumi K. Shintani¹¹ PHD, Sunil Geevarghese¹² MD, MSCI, Russell R Miller III, ¹³ MD, MPH, Angelo Canonico¹⁴ MD, Kristen Merkle³ BA, Christopher J. Cannistraci³ MS, Baxter P. Rogers², ³, ¹⁶ PHD, J. Chris Gatenby², ³, ¹⁶ PHD, Stephan Heckers¹, ² MD, MSC, John C. Gore², ³, ¹⁶ PHD, Ramona O. Hopkins⁷, ¹³, ¹⁵ PHD, E. Wesley Ely⁴-⁶, ¹⁰ MD, MPH for the VISIONS Investigation (VISualizing Icu SurvivOrs Neuroradiological Sequelae)

Under review CCM
The Association between Brain Volumes, Delirium Duration and Cognitive Outcomes in Intensive Care Unit Survivors: A Prospective Exploratory Cohort Magnetic Resonance Imaging Study

Hypotheses:
• To explore the hypothesis that increased duration of delirium in medical and surgical ICU survivors was associated with smaller brain volumes, both globally and in areas that play an important role in executive functioning (e.g., frontal lobes) and memory (e.g., hippocampus);
• To examine if brain volumes were associated with Long-Term Cognitive Impairment (LTCl) globally and in brain areas associated with executive functioning (e.g., frontal lobes), memory (e.g., hippocampus), and attention (e.g., parietal cortex, cerebellum)

Under review CCM
In 6 of 8 patients who received MRI for persistent delirium, the radiology report indicated white matter hyperintensities with different severity: Grade 1 (punctiform), Grade 2 (patchy) and Grade 3 (diffuse)
The Relationship between Delirium Duration, White Matter Integrity, and Cognitive Impairment in Intensive Care Unit Survivors as Determined by Diffusion Tensor Imaging

Alessandro Morandi¹⁻³ MD, MPH Baxter P. Rogers⁴, ⁵, ⁶ PhD, Max L. Gunther⁴, ⁵, ⁷ PhD, Kristen Merkle⁵ BA, Pratik Pandharipande⁸, ⁹ MD, MSCI, Timothy D. Girard¹⁻³, ¹⁰ MD, MSCI, James C. Jackson², ⁴, ⁷, ¹⁰ PSyD, Jennifer Thompson¹¹ MPH, Ayumi K. Shintani¹¹ PhD, Sunil Geevarghese¹² MD, MSCI, Russell R Miller III¹³ MD, MPH, Angelo Canonico¹⁴ MD, Christopher J. Cannistraci⁵ MS, Stephan Heckers ⁴, ⁷ MD, MSC, John C. Gore ⁴, ⁵, ⁶ PhD, E. Wesley Ely¹⁻³, ¹⁰ MD, MPH, Ramona O. Hopkins¹³, ¹⁵ PhD for the VISIONS Investigation (VISualizing Icu SurvivOrs Neuroradiological Sequelae)

Under review CCM
The Relationship between Delirium Duration, White Matter Integrity, and Cognitive Impairment in Intensive Care Unit Survivors as Determined by Diffusion Tensor Imaging

Hypotheses:

• Relationships between delirium duration and brain white matter integrity

• Relationships between white matter integrity and Long-term cognitive impairment (LTCI)

Under review CCM
Take Home Messages

• La medicina americana:
  – Un’utile esperienza

• La polifarmacologia post-ICU
  – Un problema emergente

• La fisiopatologia del delirium:
  – Nuove ipotesi da sviluppare e possibili trattamenti (Neuroprotezione)
  – Il ruolo del neuroimaging
“E’ una storia, quella del delirium, piena di interrogativi; è però così importante sul piano epidemiologico e significativa sul piano clinico ed antropologico da giustificare l’interesse crescente –anche se ancora non sufficiente- della letteratura”

Trabucchi M in “Il Delirium”; Morandi, Ely, Trabucchi Vita e Pensiero, in press
“….è necessario continuare lo studio senza pessimismo, ma anche senza l’illusione di arrivare a definire a breve modelli interpretativi. In attesa della risposta capace di modificare lo scenario, gli “small gains”, cioè i piccoli miglioramenti che possono essere oggi offerti al paziente che soffre, rappresentano passaggi importanti nella storia naturale della malattia e sono l’immagine di un’attenzione da parte degli operatori e della medicina nel suo insieme verso una problematica troppo spesso trascurata.”

Trabucchi M in “Il Delirium”; Morandi, Ely, Trabucchi Vita e Pensiero, in press