BIOGRAPHICAL SKETCH

NAME: Gianfranco Umberto Meduri, MD

POSITION TITLE: Professor of Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Padua U., School of Medicine, Padua, Italy	M.D.	1977	Medicine
Kettering Medical Center, Dayton, Ohio	Residency	1979-82	Internal Medicine
Memorial Sloan-Kettering Cancer Center, NY, NY	Fellowship	1982-83	Critical Care Med.
Memorial Sloan-Kettering Cancer Center, NY, NY	Fellowship	1983-85	Pulmonary Med.

Positions, Scientific Appointments, and Honors

Positions and Employment

1982-1985 Clinical Instructor in Medicine. Cornell University - New York Hospital, New York, NY.
1985-1988 Director of Clinical Research - Hinds Center for Respiratory Research/ Yale University School of Medicine Norwalk Hospital, Norwalk, CT.
1987-1988 Associate Director Pulmonary and Critical Care Fellowship Program - Norwalk Hsp., Norwalk, CT
1988-1992 Assistant Professor of Medicine - University of Tennessee Health Science Center, Memphis, TN.
1988-1996 Director of Respiratory Services, UT Bowld Hospital
1992-1997 Associate Professor of Medicine - University of Tennessee Health Science Center, Memphis, TN.
1996-2007 Director of Memphis Lung Research Program, University of Tennessee Health Science Center
1997-2022 Professor of Medicine - University of Tennessee Health Science Center, Memphis, TN.
2004-present Adjunct Professor in the Department of Pharmaceutical Sciences,
2007-2009 Director of Medical Intensive Care Unit – Memphis Veteran Administration Medical Center
2007-2021 Chair Cooperative Studies Program No. 574 (2010-2019) ESCAPe [Extended Steroid (in) CAP(e)]
2020 Founding member of the FLCC Alliance

Honors

2004 Highest individual impact factor among twenty leading critical care investigators between 1997 and August 2003 (Adams and Simonson. Publications, citations, and impact factors of leading investigators in critical care medicine. Respiratory Care 2004; 49: 276-281.)
2006 Society of Critical Care Medicine Annual Scientific Award; 2008 Trudeau Lecture Award – The New York State Thoracic Society
2008 Trudeau Lecture Award – The New York State Thoracic Society
2009 American College of Chest Physicians, in the 75th anniversary included the Chest 2007; 131: 954-963. publication as one of top 75 seminal studies published from 1934 to 2009.
2018 CHEST annual meeting, San Antonio Texas. Roger C. Bone Memorial Lecture in Critical Care.

C. Contributions to Science

Noninvasive mechanical ventilation (NPPV)

Dr. Meduri first reported on the use of NPPV in patients with acute respiratory failure (ARF) in 1989 and expanded this field with multiple prospective and randomized trials showing efficacy in both hypercapnic and hypoxemic ARF. Dr. Meduri's group reported the first large (n=164) prospective study investigating NPPV as first-line intervention in multifactorial ARF; this report has broadened the application of NPPV. Because of Dr. Meduri's work (17 publications), the methodology that he developed is now standard of practice worldwide. Multiple meta-analyses have shown that the use of NPPV is associated with a significant reduction in hospital utilization and mortality. Selected references below.

a. Meduri GU, Conoscenti CS, Menashe P, Nair S. Noninvasive face mask mechanical ventilation in acute respiratory failure. Chest 1989; 95:865-870. PMID: 2924616
b. Meduri GU, Turner R, Tolley E, Wunderink R, Abou-Shala N. Noninvasive positive pressure ventilation via face mask. First line intervention in patients with acute hypercapnic and hypoxemic acute respiratory failure. Chest 1996; 109:179-193. PMID: 8549183
c. Antonelli M, Conti G, Rocco M, Bufi M, DeBlasi RA, Vivino G, Gasparetto A., Meduri GU. A comparison of noninvasive positive pressure ventilation and conventional ventilation in patients with acute hypoxemic respiratory failure. N Engl J Med 1998; 339:429-435. PMID: 9700176
d. Meduri GU, Conoscenti CC, Menashe P. Noninvasive Mechanical Ventilation in Acute Respiratory Failure: Happy 30-YearAnniversary! Chest 2020; 157:255-257

Diagnosis and differential diagnosis of ventilator-associated pneumonia (VAP)

Dr. Meduri developed and first reported on the use of protected bronchoalveloar lavage to diagnose VAP. Dr. Meduri and colleagues organized an international consensus conference on standardizing the diagnosis of VAP in 1992 and published multiple manuscripts including the only prospective study on the differential diagnosis if VAP showing that clinical criteria are misleading and that fever in ARDS is frequently caused by pulmonary inflammation and not infection. Selected references below.

a. Meduri GU, Beals DH, Maijub AG, Baselski V. Protected bronchoalveolar lavage: A new bronchoscopic technique to retrieve uncontaminated distal airway secretions. Am Rev Respir Dis 1991; 143:855-864. PMID: 1706911
b. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. Chest 1992; 102:557-564S. PMID: 1424930
c. Meduri GU, Mauldin GL, Wunderink RG, Leeper KV, Jones C, Tolley E, Mayhall G. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest 1994: 106:221-235. PMID: 8020275
d. Meduri GU, Reddy R, Stanley T, El-Zeky F. Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. Am J Resp Crit Care Med 1998; 158:870-875. PMID: 9731019

Dysregulated systemic (cytokine storm) and pulmonary inflammation in sepsis and ARDS

Dr. Meduri's group first conducted longitudinal studies incorporating serial plasma and bronchoalveolar lavage samples and reported in 1995 that morbidity and mortality in sepsis and ARDS are the results of dysregulated systemic and pulmonary inflammation. Later, using an ex vivo model of systemic inflammation, we investigated the intracellular upstream and downstream events associated with DNA binding of NF-κB and GRα in naïve peripheral blood leukocytes (PBLs) stimulated with longitudinal plasma specimens obtained from 28 ARDS patients (most ARDS caused by sepsis). Intracellular and extracellular laboratory findings were correlated with physiological progression (resolving vs. unresolving) of ARDS in the first week of mechanical ventilation and after blind randomization to prolonged glucocorticoid treatment vs. placebo on day 9 ± 3 of ARDS. Plasma samples from patients with declining inflammatory cytokine levels (regulated systemic inflammation) over time elicited a progressive increase in all measured aspects of GC-GRα-mediated activity ($p = 0.0001$) and a corresponding reduction in NF-κB nuclear binding ($p = 0.0001$) and transcription of TNF-α and IL-1β. In contrast, plasma samples from patients with sustained elevation in inflammatory cytokine levels elicited only modest longitudinal increases in GC-GRα-mediated activity ($p = 0.04$) and a progressive increase in NF-κB nuclear binding over time ($p = 0.0001$) that was most striking in nonsurvivors (dysregulated, NF-κB-driven response).

These findings demonstrate that insufficient GC-GRα-mediated activity is an important mechanism for early loss of homeostatic autoregulation (i.e., down-regulation of NF-κB activation). Selected references below.

a. Meduri GU, Headley S, Stentz F, Kohler G, Tolley E, Leeper KV, Umberger R. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 and IL-6 are consistent and efficient predictors of outcome over time. Chest 1995; 107:1062-1073. PMID: 7705118
b. Meduri GU, Headley S, Stentz F, Kohler G, Tolley E, Postlethwaite A. Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts a poor outcome in ARDS. Chest 1995; 108:1303-1314. PMID: 7587434
c. Meduri GU, Headley S, Tolley E, Shelby M, Stentz F, Postlethwaite A. Plasma and BAL cytokines response to corticosteroid rescue treatment of late ARDS. Chest 1995; 108:1315-1325. PMID: 7587435
d. Meduri GU, Muthiah P., Carratu P, ElTorky M, Chrousos G. Nuclear factor-kappaB- and glucocorticoid receptor alpha- mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. NeuroImmunoModulation 2005; 12:321-338. PMID:16557033

Dysregulated systemic inflammation (cytokine storm) and the pathogenesis of nosocomial infections in ARDS.

The findings from Dr. Meduri's studies described above suggested that final outcome in patients with ARDS is related to the magnitude and duration of the host inflammatory response, and that intercurrent nosocomial infections might be an epiphenomenon of prolonged intense inflammation. Dr. Meduri hypothesized that cytokines secreted by the host during ARDS may indeed favor the growth of bacteria and explain the association between an exaggerated and protracted release of cytokines and the frequent development of nosocomial infections. The Memphis Lung Research Program laboratory conducted *in vitro* studies evaluating the extracellular and intracellular growth response of three clinically relevant bacteria in response to graded concentrations of proinflammatory cytokines TNF–α, IL–1β, and IL–6. The bacteria used were fresh isolates of *Staphylococcus aureus*, *Pseudomonas aeruginosa,* and *Acinetobacter* sps. obtained from patients with ARDS. In these studies, the investigators identified a U-shaped response of bacterial growth to proinflammatory cytokines. When the tested bacteria were exposed *in vitro* to a lower concentration (10 pg to 250 pg) of TNF–α, IL–1β, or IL–6—similar to the plasma values detected in ARDS survivors—extracellular and intracellular bacterial growth was not promoted, and human monocytic cells were efficient in killing the ingested bacteria. On the contrary, when bacteria were exposed to higher concentrations of these of proinflammatory cytokines—similar to the plasma values detected in ARDS nonsurvivors—intracellular and extracellular bacterial growth was enhanced in a dose-dependent manner. Blockade by specific neutralizing monoclonal antibodies (MoAb) significantly inhibited cytokine-induced extracellular and intracellular bacterial growth. In another series of experiments, we found that impairment in intracellular bacterial killing correlated with the increased expression of proinflammatory cytokines, while restoration of monocyte killing function upon exposure to methylprednisolone coincided with the downregulation of the expression of TNF–α, IL–1β, and IL–6. Selected references below.

a. Meduri GU, Tolley EA, Chrousos G, Stentz F. Prolonged methylprednisolone treatment suppress systemic inflammation in patients with unresolving ARDS: Evidence of inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoid. Am J Respir Crit Care Med 2002; 165:983-991. PMID: 11934726
b. Sinclair S, Bijoy J, Golden E, Carratu P, Umberger R, Meduri GU. Interleukin-8 and Soluble Intercellular Adhesion Molecule-1 during acute respiratory distress syndrome and in Response to Prolonged Methylprednisolone Treatment. Minerva Pneumologica 2006; 45(2):93-103. https://www.minervamedica.it/en/journals/minerva-pneumologica/article.php?cod=R16Y2006N02A0093
c. Seam N, Meduri GU, Wang H, Nylen ES, Sun J, Schultz MJ, Tropea M, Becker KL, Suffredini AF. Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early ARDS. Critical Care Medicine 2012: 40:495-501. PMID: 21983371
d. Narute P, Seam N, Tropea M, Logun Ca, Rongman Cai, Sun J, Shelhamer JH, Meduri GU, Suffredini AF. Temporal changes in microRNA expression in blood leukocytes from patients with the acute respiratory distress syndrome. Shock 2017; 47:688-695. PMID: 27879560

Modulation of systemic inflammation by prolonged glucocorticoid treatment in ARDS

Dr. Meduri's group has collected serial plasma and BAL samples in ARDS patients recruited in a randomized trial investigating prolonged methylprednisolone treatment (PMT). In an ex-vivo study, we have shown that PMT – contrary to placebo – was associated with upregulation in GRα number and nuclear translocation with reduction in NF-κB DNA-binding and transcription of inflammatory cytokines. ARDS patients randomized to PMT, contrary to placebo, demonstrated a sustained reduction in plasma and/ or BAL levels of TNF-α, IL-1β, IL-6, IL-8, soluble intercellular adhesion molecule-1, procollagen aminoterminal propeptide type I and III, indices of alveolar-capillary membrane permeability (BAL albumin, total protein, and percentage neutrophils), and an increase in IL-10 and protein C. Selected references below.

a. Meduri GU, Tolley EA, Chrousos G, Stentz F. Prolonged methylprednisolone treatment suppress systemic inflammation in patients with unresolving ARDS: Evidence of inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoid. Am J Respir Crit Care Med 2002; 165:983-991. PMID: 11934726
b. Sinclair S, Bijoy J, Golden E, Carratu P, Umberger R, Meduri GU. Interleukin-8 and Soluble Intercellular Adhesion Molecule-1 during acute respiratory distress syndrome and in Response to Prolonged Methylprednisolone Treatment. Minerva Pneumologica 2006; 45(2):93-103. https://www.minervamedica.it/en/journals/minerva-pneumologica/article.php?cod=R16Y2006N02A0093
c. Seam N, Meduri GU, Wang H, Nylen ES, Sun J, Schultz MJ, Tropea M, Becker KL, Suffredini AF. Effects of methylprednisolone infusion on markers of inflammation, coagulation, and angiogenesis in early ARDS. Critical Care Medicine 2012: 40:495-501. PMID: 21983371
d. Narute P, Seam N, Tropea M, Logun Ca, Rongman Cai, Sun J, Shelhamer JH, Meduri GU, Suffredini AF. Temporal changes in microRNA expression in blood leukocytes from patients with the acute respiratory distress syndrome. Shock 2017; 47:688-695. PMID: 27879560

Randomized trials (RCTs) investigating prolonged glucocorticoid treatment in severe pneumonia and ARDS

Dr. Meduri has designed and published proof of concept observational studies providing a rationale for prolonged glucocorticoid treatment in ARDS. In these studies, we have determined that four critical components of treatment affect the beneficial effects of prolonged glucocorticoid therapy - timing of initiation, dosage, duration of treatment including tapering, and mode of delivery - and by the implementation of preventive measures to minimize potential complications. These findings were incorporated in the design of RCTs. I have designed and conducted RCTs investigating prolonged low dose glucocorticoid treatment in patients with (i) severe pneumonia (collaboration with Dr. Marco Confalonieri in the landmark first RCT investigating hydrocortisone in severe CAP, and ESCAPe trial (complete in 2017 – see below), (ii) early severe ARDS, and (iii) unresolving ARDS. In a recent meta-analysis, we have demonstrated prolonged methylprednisolone treatment accelerates resolution of ARDS (increased MV [13.3 ± 11.8 vs. 7.6 ± 5.7; p<0.001] and ICU-free days [10.8 ± 0.71 vs. 6.4 ± 0.85; p<0.001] - and decreasing hospital mortality (36% vs. 49%, risk ratio 0.76, 95% CI 0.59-0.98, I^2 17%, p=0.035; moderate certainty) and health care utilization. At present, I am the Chair of VA Cooperative Studies Program #574 "A Randomized, Placebo-Controlled, Double-Blind Clinical Trial to Evaluate the Safety and Efficacy of Methylprednisolone in Hospitalized Veterans with Severe Community-Acquired Pneumonia" (CSP #574). Selected references below.

a. Meduri GU, Headley S, Golden E, Carson S, Umberger R, Kelso T, Tolley E. Effect of prolonged methylprednisolone therapy in unresolving ARDS. A randomized controlled trial. JAMA 1998; 280:159-165.
b. Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, Della Porta R, Umberger R, Meduri GU. Hydrocortisone infusion for severe community-acquired pneumonia: A preliminary randomized study. Am J Respir Crit Care Med 2005; 171:242-248.
c. Meduri GU, Golden E, Freire AX, Taylor E, Zaman M, Carson S, Gibson M, Umberger R. Methylprednisolone infusion in early acute severe ARDS: Results of a randomized controlled trial. Chest 2007; 131:954-963.
d. Meduri GU, Bridges L, Shih MC, Marik P, Siemieniuk RAC, Kocak M. 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. Intensive Care Medicine 2016; 42:829-840.

e. Meduri GU, Bridges L, Siemieniuk RAC, Kocak M. An exploratory re-analysis of the randomized trial on Efficacy of Corticosteroids as Rescue Therapy for the Late Phase of Acute Respiratory Distress Syndrome. Crit Care Med 2018; 46: 884-891.
f. Meduri GU, Shih MC, Bridges L, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. *Intensive Care Med.* 2022;48(8):1009-1023.

Reviews, observational and randomized trials (RCTs) investigating prolonged glucocorticoid treatment in severe COVID-19 pneumonia and ARDS.

a. Chrousos G, Meduri GU Critical COVID-19 disease, homeostasis, and the "surprise" of effective glucocorticoid therapy. Clinical Immunology 2020 https://doi.org/10.1016/j.clim.2020.108550.
b. Villar J, Confalonieri M, Pastores S, Meduri GU. Rationale for Prolonged Corticosteroid Treatment in the Acute Respiratory Distress Syndrome Caused by Coronavirus Disease 2019. Crit Care Explor 2020; 2: e0111 PMID: 32426753
c. Marik PE, Kory P, Varon J, Iglesias J, Meduri GU. MATH+ protocol for the treatment of SARS-CoV-2 infection: the scientific rationale. Expert Review of Anti-infective Therapy. Published online: 18 Aug 2020. PMID: 32809870
d. Salton F, Confalonieri P, Meduri GU, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. *Open Forum Infectious Diseases.* 2020;7(10):ofaa421
e. Salton F, Confalonieri P, Centanni S, et al. Prolonged higher dose methylprednisolone vs. conventional dexamethasone in COVID-19 pneumonia: a randomised controlled trial (MEDEAS). Eur Respir J. 2022.
f. Salton F, Confalonieri P, Campisciano G, et al. Cytokine Profiles as Potential Prognostic and Therapeutic Markers in SARS-CoV-2-Induced ARDS. Journal of Clinical Medicine. 2022;11(11):2951.

New understanding on the general adaptation in critical illness and the fundamental role of prolonged glucocorticoid treatment with micronutrient supplementation in disease resolution

a. Meduri GU, Chrousos GP. General Adaptation in Critical Illness: Glucocorticoid Receptor-alpha Master Regulator of Homeostatic Corrections. Front Endocrinol (Lausanne). 2020;11(161):161.
b. Meduri GU, Chrousos GP. General Adaptation in Critical Illness: Glucocorticoid Receptor-alpha Master Regulator of Homeostatic Corrections. Front Endocrinol (Lausanne). 2020;11(161): 161.Meduri GU, Confalonieri M, Chaudhuri D, Rochwerg B, Meibohm B. Prolonged glucocorticoid treatment in ARDS: pathobiological rationale and pharmacological principles. In: Fink G, ed. Handbook of Stress: Stress, Immunology and Inflammation. Vol 5. Academic Press; 2023.
c. Meduri GU, Psarra A-M, Amrein K. General Adaptation in Critical Illness 2: The Glucocorticoid Signaling System as a Master Rheostat of Homeostatic Corrections in Concerted Action with Mitochondrial and Essential Micronutrient Support. In: Fink G, ed. Handbook of Stress: Stress, Immunology and Inflammation. . Vol 5. Academic Press; 2023.
d. Meduri GU, Chrousos GA. General Adaptation in Critical Illness: The Glucocorticoid Signaling System as Master Rheostat of Homeostatic Corrections in Concerted Action with Nuclear Factor-kB. In: Fink G, ed. Handbook of Stress: Stress, Immunology and Inflammation. . Vol 5. Academic Press; 2023.
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Complete List of Published Work Cited in 28100 medical publications.

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https://www.ncbi.nlm.nih.gov/pubmed/?term=meduri+gu[author]