

# **The Destruction of the Memphis Lung Research Program and the Global Human and Economic Repercussions**

*This timeline provides a much-abbreviated synopsis of the unpublished actions of a scientific institution of health in the United States that blocked the progress of inexpensive and life-saving treatment — while fully aware of the dire consequences to public health.*

*These actions, which began in 2001 in Memphis, Tennessee, are directly responsible for the deaths of hundreds of thousands from 2002-2020; and millions more during the first year of the COVID-19 pandemic. If not for these actions, most of those who perished around the world would have been saved and the economy's collapse significantly mitigated.*

*The public has a right to know.*

# **THE WHISTLEBLOWER**

## **Dr. G. Umberto Meduri**

From 1988-2022, Dr. G. Umberto Meduri was a tenured Professor in the Department of Medicine at the **University of Tennessee Health Science Center (UTHSC)** in Memphis. Dr. Meduri, a prolific research scientist, has conducted clinical and translational research on corticosteroid treatment of Acute Respiratory Distress Syndrome (ARDS; see appendix) and severe pneumonia (two of the leading causes of death in the US) and is recognized as the world's leading expert in this field. He was the director of the **Memphis Lung Research Program (MLRP)** at UTHSC and is globally recognized as the pioneer of noninvasive ventilation. A 2021 commentary in JAMA Internal Medicine (18:478-479) titled "Decreased COVID-19 Mortality—A Cause for Optimism" highlighted corticosteroid treatment and noninvasive ventilation as two of the few interventions that have been proven to decrease mortality in hospitalized patients with severe COVID-19.

**What are corticosteroids?** Corticosteroids, also called glucocorticoids, are hormones produced by the body during times of stress and are essential for critical illness support. Dr. Meduri's research has shown that inadequate activation of the corticosteroid receptor pathway is a leading mechanism of death in ARDS. Methylprednisolone, dexamethasone, and hydrocortisone are all effective corticosteroid compounds that have been available for over 50 years. Dr. Meduri's translational studies have demonstrated that low-dose methylprednisolone treatment can safely and effectively reverse the disease processes in ARDS.

## 1992-2002

- At UTHSC, Dr. Meduri's group researched methylprednisolone (a corticosteroid) treatment for *late* ARDS (seven days after disease onset) and *early* ARDS (within three days of disease onset) and the role of dysregulated inflammation ("cytokine storm") in ARDS. **Severe COVID-19 pneumonia is a form of ARDS.** (See Appendix 1, which explains ARDS.)
- The MLRP reported that, in ARDS and severe infections, the primary mechanism for excessive inflammation-associated complications and death is insufficient intracellular corticosteroid action. **MLRP's research proved that corticosteroid supplementation could restore the vital functions of intracellular corticosteroids.**
- In 1998, Dr. Meduri's team at UTHSC published in the Journal of the American Medical Association (JAMA) the positive findings of a randomized controlled trial (RCT) investigating methylprednisolone in *late* ARDS.
- Translational research conducted on blood samples collected during the trial demonstrated the importance of the corticosteroid receptor pathway in ARDS' resolution, providing the most robust scientific foundation for corticosteroid treatment in ARDS and critical illness. These studies directly challenged a new pharmaceutical product and its potential market. Unfortunately, the destruction of the MLRP resulted in the loss of crucial resources and expertise, which hindered further progress in this field.
- These studies also indicated that early intervention could be more effective, leading to a new trial (see below).

## 2001

- In 2001, the MLRP was completing a RCT investigating methylprednisolone in the early onset of ARDS. Unknown to Dr. Meduri, the study was already reaching significance for mortality reduction (***see below***). Also, two large positive RCTs in patients with severe sepsis (infection) were submitted to the New England Journal of Medicine (NEJM)— one from Eli-Lilly (Xigris®) and one from France, investigating a corticosteroid (hydrocortisone).
- The NEJM rapidly published the Xigris® results — but rejected, after withholding the study for 11 months, the competing French corticosteroid treatment trial ***three days after the FDA approved Xigris®*** (later withdrawn

from the market in 2011.) (NOTE: JAMA would publish the French Trial ten months later.)

- Dr. Meduri requested that the FDA compare corticosteroids (off-patent, inexpensive drugs with a high safety profile) and Xigris<sup>®</sup>, **a human-activated Protein C drug, which is expensive and had known serious side effects**. The FDA ignored information provided by Dr. Meduri and by the French group.
- Meanwhile, UTHSC faculty, **with prior knowledge of the MLRP's RCT positive findings**, began a deliberate effort to destroy Dr. Meduri's research— just as Eli Lilly's Xigris<sup>®</sup> drug received FDA approval. **Corticosteroids are an off-patent cheap pharmacological competitors to**
- After the FDA approved Xigris<sup>®</sup>, Tom Burton, a prominent reporter from The Wall Street Journal (WSJ), contacted Dr. Meduri and planned a visit to the MLRP. Those involved in destroying the MLRP had knew of the fact.
- In December, the DSMB monitoring the early ARDS RCT obtained data showing **that methylprednisolone had, in comparison to the placebo, twice the rate of lung improvement and produced a 50% relative reduction in ICU mortality**.
- Within days, the Vice-Chancellor for Research and the Assistant General Counsel secretly handwrote a plan for an investigation on scientific misconduct and then pressured to a former MLRP's member to ~~of the~~ submit charges of alleged misconduct in Dr. Meduri's 1998 JAMA paper - assuring that they will "*control the process.*" Before proceeding, the former MLRP's member met with the site investigator for Eli Lilly's Xigris<sup>®</sup> drug, to discuss the "allegations."

## 2002

- Tom Burton, a prominent reporter from *The Wall Street Journal* (WSJ) visited Dr. Meduri's program to write a report on his ongoing research. The article (and a photo of Dr. Meduri) appeared on **the front page of the WSJ** on May 17, 2002, with the headline, "***Why Cheap Drugs That Appear to Halt Fatal Sepsis Go Unused.***" (See Appendix 2.)
- Within days of the WSJ publication (but before the submission of misconduct allegations), the **UTHSC removed the primary research funding source for Dr. Meduri's MLRP**, in violation of both university and federal regulations.

- Then, without warning, charges of scientific misconduct were leveled against Dr. Meduri by UTHSC written in a haphazard way, disorganized, and without any supporting evidence —which would ultimately lead to UTHSC’s success in destroying Dr. Meduri’s work and shutting down the MLRP. The person that put pressure to obtain charges not only assisted in writing the charges but became the chair of the inquiry committee and secretly communicated with the complainant throughout the process. **An absolute farce.** The inquiry moved to an investigation ignoring Dr. Meduri’s seventeen formal requests to receive evidence.
- **While the investigatory board found no misconduct, the deliberation was delayed to exceed the statute of limitations.** Most astonishingly, the day Dr. Meduri refused to sign a waiver of liability against the complainant and the institution, the tainted Chair changed the report findings from “*no misconduct*” to “*misconduct*”— and removed all of the scientific evidence Dr. Meduri and others provided to the board. Dr. Meduri was notified of this by the Assistant General Counsel (later disbarred), the de-facto counsel for the university, and the complainant with a vested interest in a “*misconduct*” finding to achieve a legal advantage in the upcoming litigation.
- The UTHSC Dean of Medicine requested that Dr. Meduri retract both his prior published research in corticosteroid treatment and close his ongoing research. Dr. Meduri refused.
- Dr. Meduri submitted a legal complaint to the **Claims Commission for the state of Tennessee Western Division** (Claim No. 20301720) to protect his lifesaving research.
- While research in Memphis was blocked, Dr. Meduri’s collaboration with an Italian research group continued leading to the completion and publication (2005) of the first preliminary RCT investigating corticosteroid (hydrocortisone) treatment in severe pneumonia, showing a significant mortality reduction. **In 2023, a French group published a large confirmatory RCT demonstrating that, in severe pneumonia, hydrocortisone treatment is safe and leads to a nearly fifty percent reduction in mortality. These findings will have a significant global impact.**

## 2003

- In May 2003, during the SARS pandemic, **leading Canadian experts and NIH leaders begged the UTHSC Chancellor to release the findings of Dr. Meduri's early ARDS RCT**— without success.

## 2004

- In videotaped testimony to the *Claims Commission of the State of Tennessee Western Division*, the former statistician testified that **she provided inaccurate data and distorted the writing of Dr. Meduri's study** of methylprednisolone with the intent to generate false charges.
- After the testimony, the UTHSC counsel met with Dr. Meduri and his counsel to initiate a settlement.
- After an international appeal supporting Dr. Meduri by renowned academicians and an external expert review, the UTHSC Chancellor finally cleared Dr. Meduri. However, the UTHSC did not inform the faculty or the foundations that supported his research and failed to take action to restore Dr. Meduri's severely damaged reputation (as required by its regulations.)
- Additionally, the UTHSC Assistant General Counsel retaliated by instigating the two complainants to resubmit the false charges to different federal agencies (**Office for Human Research Protections (OHRP) and the Veteran's Administration**). Despite Dr. Meduri's ample documentation of UTHSC's failure to comply with UTHSC and federal regulations, the **Office of Research Integrity (ORI)** refused to investigate the University and allowed the widespread retaliation against Dr. Meduri to continue until 2019.

## 2006

- In 2006, the **National Heart, Lung, and Blood Institute (NHLBI) ARDS Network** published a study purportedly “designed” to validate the results of Dr. Meduri's 1998 RCT on late ARDS. The study protocol, however, had **severe methodological failures, and five patients died**. Moreover, the report severely misrepresented the actual positive findings as later demonstrated by a re-analysis of the data published in 2018. The report of the flawed study was rapidly accepted by the NEJM, while the journal

concurrently rejected the submission of Dr. Meduri's positive trial investigating methylprednisolone in early ARDS. Sounds familiar?

## 2007

- Dr. Meduri's study on methylprednisolone in early ARDS was finally published in 2007 in **Chest**. It was included in international guidelines for corticosteroid use in critical illness the following year. (NOTE: The trial's findings were published with a five-year delay owing to UTHSC's unlawful defunding of Dr. Meduri's MLRP in 2002.)

## 2020

- On April 6, 2020, Drs. Meduri, Villar, and colleagues published, "*Rationale for prolonged corticosteroid treatment in the Acute Respiratory Distress Syndrome (ARDS) caused By Covid-19.*" (NOTE: A prior submission to a leading journal was rejected on March 27, 2020, because it criticized the WHO's approach.)
- The publication exposed the fallacies and potential harm of the WHO statement of "*not recommending the routine use of corticosteroids for the treatment of viral pneumonia outside clinical trials.*" The recommendation relied on an anemic, biased, and incomplete analysis of the literature. The WHO's analysis ignored the positive findings of two large studies (7,300 patients) that reported a significant reduction in mortality with dosage and duration of corticosteroids similar to the one of Dr. Meduri's RCTs.
- On April 28, 2020, a seminal transcriptomics study analyzed gene expression pathways induced by SARS-CoV-2 to identify, amongst the 5694 FDA-approved drugs, those that could be repurposed to help COVID-19 patients with severe symptoms related to hyper-inflammation. **They found methylprednisolone to be the drug with the most significant potential to reverse the changes induced by COVID-19; five independent validation data sets confirmed the results.**
- On June 16, 2020, **The Recovery Collaborative Group** (England) published a large, randomized trial showing that dexamethasone, the corticosteroid molecule also used in a 2020 Spanish trial, was associated with a significant reduction in mortality by 1/3 for those with ARDS and by 1/5 in patients requiring oxygen. **Corticosteroid treatment is the most effective therapy**

found to improve severe COVID-19 outcomes. The UK *Research and Innovation* program reported that corticosteroids saved one million COVID-19 patients in the first nine months of its implementation.



# GLOBAL IMPACTS OF THE DESTRUCTION OF THE MEMPHIS LUNG RESEARCH PROGRAM

- The widespread defamation of Dr. Meduri devastated support for corticosteroid research for ARDS. This undermined corticosteroids as a treatment for ARDS, aborted further corticosteroid research, and halted the accumulation of clinical data from RCTs. As a result of the misinformation campaign against corticosteroid treatment by the NHLBI and the (pharmaceutical industry-supported) critical care medicine leadership, there would be no further research on corticosteroids in the U.S. and Canada until 2020.
- Since the closure of the **MLRP** in 2002, only two RCTs have been conducted in the world — in Thailand and Spain. Dr. Villar and colleagues' 2020 Spanish RCT provided final definitive evidence that prolonged corticosteroid treatment is safe and effective in ARDS, decreasing ventilator dependence and mortality, providing the rationale for the Recovery Collaborative Group's trial.
- The destruction of the research program at **MLRP** has irreparably damaged progress in this life-saving research that would have led to new understandings of how to use corticosteroids most effectively, thereby saving the lives of hundreds of thousands of ARDS patients in the U.S. alone.
- Progress in **MLRP**-conducted research would have also resulted in billions of dollars saved yearly in health care utilization and fewer widows and orphans.

## **HUMAN COST**

### **THE DELAYED RECOMMENDATION FOR CORTICOSTEROID TREATMENT IN COVID-19 CAUSED HUNDREDS OF THOUSANDS OF LIVES TO BE LOST.**

- It took the WHO seven months (January 28 to September 2, 2020) to recommend corticosteroids for COVID-19 disease. **During that period of time, hundreds of thousands of patients throughout the world died from COVID-19-associated ARDS, suffering massive lung inflammation.** These patients were denied corticosteroid therapy partly because of the defamation of Dr. Meduri's research and misrepresentation of the NHLBI-ARDS Network trial results in the **NEJM**. Evidence from prior viral pandemics – SARS, H1N1, MERS — supported the effectiveness of corticosteroids, but RCTs were missing. **Months before the WHO's recommendation, the Front Line COVID-19 Critical Care (FLCCC) Alliance (www.flccc.net) was the only organization recommending corticosteroid treatment for severe COVID-19 in the U.S.**
- **From 2002-2020, hundreds of thousands of patients with severe viral infections such as H1N1, SARS, MERS, and COVID-19 would have had a much higher chance of survival.** During COVID, treatment with corticosteroids would have mitigated the social and economic costs of the pandemic. Progress generated by the **MLRP's** research could have prevented all of this.

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*This is an abbreviated compendium of the facts in this case. All of the facts in this and supporting documents (available upon request) are objective and verifiable. Much of what is outlined in this document originates from the affidavit and exhibits submitted to **the Claims Commission of the State of Tennessee Western Division (Claim No. 20301720)** on or before August 12, 2008.*

## **Appendix 1**

### **What is ARDS?**

ARDS is the most severe form of acute lung disease. The lungs are the organ with the broadest vascular surface to facilitate the entrance of oxygen into the body. In ARDS, massive inflammation within the systemic circulation and widespread leak of blood vessels in the lungs cause the flooding of air sacs and the inability to oxygenate the blood. Consequently, mechanical ventilation is required to support life.

The leading precipitating causes of ARDS are severe infections and severe sepsis—most frequently pneumonia. COVID-19-associated ARDS is the leading cause of death for COVID-19 hospitalized patients requiring mechanical ventilation. ARDS is associated with high hospital mortality and long-term disability (correlating with mechanical ventilation duration) in survivors, which often correlates with the duration of mechanical ventilation required to support life.

## **Appendix 2**

### **Fallacies in the WHO statement of “not recommending the routine use of corticosteroids for treatment of viral pneumonia outside clinical trials.”<sup>1</sup>**

Source: *“Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome (ARDS) caused By Covid-19.”<sup>2</sup>*

The publication exposed the fallacies and potential harm of the WHO statement of *“not recommending the routine use of corticosteroids for treatment of viral pneumonia outside clinical trials.”* The recommendation relied on an anemic, biased, and incomplete literature analysis.<sup>3</sup> The WHO’s *“conclusive”* statement rested on only four studies without including results from another 25 publications.<sup>4</sup> Six of the 10 studies in the referenced meta-analysis did not describe the type of corticosteroid used.<sup>5</sup> The alleged complications of corticosteroid treatment occurred only in the subgroup of patients receiving a very high dose (3-4 times the one recommended by the Task Force for ARDS);<sup>6-8</sup> and this essential information was not provided. Second, the WHO’s analysis ignored the positive findings of three large studies [5327<sup>9</sup> and 401<sup>10</sup> patients with severe acute respiratory

syndrome (SARS) and 2141 patients with influenza H1N1 pneumonia <sup>11]</sup> that evaluated the impact of time, dose, and duration of CST and reported a significant reduction in mortality with dosage and duration similar to the one recommended by SCCM and ESICM Task Force.<sup>12</sup> The WHO Task Force also failed to report that in one large H1N1 study [n = 2141], patients receiving low-to-moderate dose corticosteroid achieve a fifty percent relative reduction in mortality. Finally, the WHO report misrepresented the literature on the impact of corticosteroid treatment on viral clearance. The referenced article<sup>13</sup> reported (i) a reduction in clearance for corticosteroid treatment of fewer than seven days, while (ii) a treatment duration of greater than seven days (the one recommended for ARDS and COVID-19) was associated with a fifty percent reduction in mortality and had no negative impact on viral clearance.

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## Left on the Shelf

### Why Cheap Drugs That Appear To Halt Fatal Sepsis Go Unused

**Steroids Need Big Human Trial, But Pharmaceutical Makers Lack Incentive to Fund One**

**Dr. Meduri's 15-Year Quest**

By Thomas M. Herten

It was strictly hypochondria that was the doctor off on his quest, a young mother honoring her death in a Connecticut hospital was misdiagnosed, and given a drug she wouldn't otherwise have gotten. She recovered.

Then the doctor, G. Umberto Meduri, learned that what the woman actually had was sepsis, a devastating condition that has long been on his mind as a doctor. It has long been on his mind as a doctor. It has long been on his mind as a doctor.

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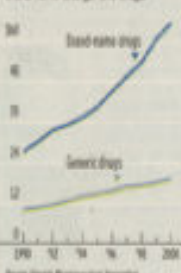
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### Widening Gap

Average retail prescriber price of brand-name and generic drugs



only approved for sepsis in about \$7,000 a dose.

The drug, Eli Lilly & Co.'s newly approved Xigris, was the first of large studies involving hundreds of millions of dollars, and Lilly is spending lavishly to promote it. The Meduri approach emphasizes, however, that even the large-scale studies that most doctors need to be convinced.

The steroid saga illustrates the massive expense brand-name drugs don't face when competing from low-priced generics. There is little incentive for pharmaceutical companies—the main financiers of drug research—to pay for studies of using steroids against sepsis, because the steroid patients have enjoyed. The National Institutes of Health also funded Dr. Meduri's work, not human trials of drugs.

Dr. Meduri, who finally got modest funding from a church-affiliated health-care foundation in Tennessee, has recently had to slash the size of what he hoped would be a major study, as his funding ran low. He has had of some researchers and the last use of his laboratory at the University of Tennessee resigned Dr. Sifting in fromers are thousands of blood-plasma samples that might reveal which patients profited most from the steroid.

"Meduri has been a money-crying in the wilderness," says John J. Marini, a University of Tennessee professor and co-author of a paper in *Journal of Intensive Care Medicine*.

## Why Low-Cost Drugs That Might Halt Deadly Sepsis Go Unused

Continued From First Page

city of Massachusetts medical professor and operated in critical care. "The data are intriguing, and consistent with my clinical experience. However, these vitamins that steroids have used patients in my area."

It's a Catch-22: Because steroids are available, only small studies are possible. Because they are small, they are viewed as less than convincing, allowing skepticism to persist—and money to remain available. The drug that drew the attention of the team's research and provided money for the steroid was, which are also for more expensive.

By all accounts, the paper didn't do it. Gordon G. Bernard, a professor at Vanderbilt University critical-care specialist, he was the chief investigator both on a 1997 study showing steroids ineffective, and on the study he is now studying at Lilly's request. Dr. Bernard has been unable to do a study of Dr. Meduri's work, although he is usually personal terms. In a medical conference debate with Dr. Meduri at the University of Texas at Dallas, for instance, Dr. Bernard argued to persuade Dr. Meduri's team that the steroid was not as effective as he claimed.

Dr. Bernard says he regrets his 1997 results, as for whether steroids used the way Dr. Meduri proposes could help with sepsis. He says it's a fair judgment—but give me some data.

Sepsis—what doctors call the "big one" when a newspaper says someone died of "complications" from surgery or illness—is an average of every body as well as an illness. It's a complex of symptoms, and the symptoms are at the University of Tennessee, and the symptoms are at the University of Tennessee, and the symptoms are at the University of Tennessee.

The story suggests why again and the steroid-related acute respiratory distress syndrome have emerged in the past. It's a complex of symptoms, and the symptoms are at the University of Tennessee, and the symptoms are at the University of Tennessee.

Out of Control

The body's reaction to bacterial invaders such as the. One's with inflammation, a response that is normally beneficial, but becomes harmful. The inflammation causes the body to release a signaling chemical instead of a steroid. It can cause the lung, the large or other organs to swell shut down.

The body normally regulates inflammation by releasing steroid. A signal sent from the pituitary gland to the adrenal gland, which produces cortisol, tells the adrenal gland to produce cortisol. The cortisol then acts on the body's cells to reduce inflammation.

### How Sepsis Can Occur

What happens when an infection invades the body and how it can lead to sepsis, using the example of a respiratory infection.

1. Bacterial products or other inflammatory agents enter the lungs, activating a protein called TNF, which stimulates the production of "fighting" proteins called cytokines.
2. These cytokines set off the inflammation in organs. The resulting inflammation can be fatal, but if contained, inflammation can be the cause of other organ damage.
3. After cytokines reach the brain's pituitary gland, it releases a hormone called ACTH.
4. ACTH flows through the bloodstream and stimulates the adrenal gland to produce a steroid called cortisol.
5. Cortisol affects the cell proteins, which gives cortisol its effects, including the ability to reduce inflammation. When the inflammation subsides, the cytokines, which were released to fight the infection, also subside, allowing the body to heal itself.

Source: Meduri et al., *New England Journal of Medicine*



But, the most prominent of which was published by Vanderbilt's Dr. Bernard.

The approach of Dr. Meduri and others at the University of Tennessee is to use steroids for days or weeks, not just for a few days. They believe steroids can be used for a longer period of time, and that this approach is more effective than the standard approach of using steroids for a few days.

The story later went, what helped Gray Morrow Jr., a retired accountant and owner in Greenville, S.C., who had a heart attack in 1998. Dr. Meduri's approach was to use steroids for a longer period of time, and that this approach is more effective than the standard approach of using steroids for a few days.

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### DRUG PRICES

Why They Keep Soaring

Fourth in a Series

Why you're paying more for your drugs, says Dr. Meduri, who is now at the University of Tennessee Health Science Center in Memphis.

What followed was 11 years of battling the forces of medicine that seemed to be with what happened in the Connecticut hospital. Now, Dr. Meduri and colleagues in the U.S. and Europe have accumulated a modest body of evidence that the deadliest forms of sepsis often yield to cheap, common steroids such as cortisone.

It is the deadliest form of sepsis, a severe form of sepsis in which blood pressure plunges. If the approach is not effective, it could be big economic news. It typically costs less than \$10. The only drug speci-

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