Jeffrey M. Drazen, M.D.
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860 Winter Street
Waltham, MA 02451-1413

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Dear Editor:

We would like to request that the New England Journal of Medicine undertake an evaluation of the "REDUCE MRSA" manuscript by Huang, et al.,[1] for consideration of retraction due to a variety of concerns which we feel impact the integrity of this research. We feel this reexamination is of paramount importance, since we believe that the REDUCE MRSA manuscript has led to an overestimation on the efficacy of Chlorhexidine in the prevention of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections and has formed the basis for policy recommendation regarding control of MRSA. Of grave concern is mounting evidence that Chlorhexidine may promote bacterial resistance to antibiotics.

Spinning of Results in the Abstract of The Paper:

- As described in Kavanagh, et al., "The abstract stated that MRSA screening and isolation were 'implemented' in group 1 and that there was a little reported difference between the intervention and baseline periods in MRSA clinical isolates (3.2 versus 3.4 per 1000 days)." [2] We feel the use of the word "implemented" is confusing and might lead one to conclude that active detection (screening) and isolation was ineffective. However, there was no difference in how the subjects were treated between the baseline and intervention arms, both underwent screening and isolation. Group 1 was used to control for changes over time.

- The Reduce MRSA Study's Abstract Concludes: "In routine ICU practice, universal decolonization was more effective than targeted decolonization or screening and isolation in reducing rates of MRSA clinical isolates and bloodstream infection from any pathogen."[1]

  However, Kavanagh, et al., points out that "The largest area of significant reduction was with a reduction in infections in the "Any Pathogen" metric, but the organisms that accounted for the vast majority of the reduced infections were skin commensal bacteria. " [3]

  Thus, "any pathogen" does not mean "ALL" pathogens but apparently is referring to a composite metric which groups many different types of bacteria together.

Changing of Metrics: The REDUCE MRSA Study had multiple metrics changes on ClinicalTrials.gov. The metric for urinary tract infections was present, eliminated, then added back again. The explanation for the elimination of CLABSIs was given then the explanation was retracted. A new metric which combined categories was also added after the trial completion date. We feel that any changes in metrics after the trial initiation date should be a cause of concern.

- 2009, Sept. 19: ClinicalTrials.gov. HCA listed as a partner with the CDC for the Study[4]
  -- First Received Study –Sept. 19, 2009.
  -- Study Start Date. Sept. 2009

- 2011, Sept.: Study Completion Date and Primary Completion Date (Last Collection of Data for Primary Outcome Measure)[4]

- 2012, Mar. 7: AHRQ Task Order for Analysis and Dissemination of the Results.[5]
  -- Secondary Outcome Evaluation – Central Line-Associated Blood Stream Infections.
  -- Secondary Outcome Evaluation – Nosocomial Bloodstream and Urine Infections.

- 2012, Jun., 19: Clinical Trials.gov.[6]
  -- Elimination of the "Urinary Cultures" metric.
  -- Elimination of "Routinely reported central line blood stream infections (CLABSI)" metric.
  -- Addition of "ICU-attributable All-pathogen Bloodstream Infection" metric (a composite category)

- 2013, May 29: REDUCE MRSA Study Published in the NEJM.[1]

- 2013, Oct. 7: Commentary by Kavanagh, et al published online which discussed changes in metrics which occurred in the REDUCE MRSA Study.[7]

- 2014, April: Response by Huang and Platt stating "All secondary outcomes were declared prior to the completion of the trial and prior to performing any analyses" [8] The paper references the March 7, 2012 AHRQ Task Order.[5]

  Although the "All-pathogen Bloodstream Infection" metric was declared (nosocomial bloodstream infections) in the Mar. 2012 task order, so were the metrics for CLABSIs and Urine Infections. In June of 2012, these two latter metrics were eliminated on ClinicalTrials.gov (after the date of the task order).

- 2013, Oct. 16: ClinicalTrials.gov.[6]
  -- Reason for CLABSI Elimination Given. ("Note: CLABSI outcome was dropped due to an inability to acquire standardized denominators for this measure. ")
  -- Added "Urinary tract infections" metric.
  -- Added "Emergence of resistance to mupirocin and chlorhexidine" metric.
  -- Added "Blood culture contamination" metric.
  -- Added "Cost effectiveness" metric.

- 2014, July 7: ClinicalTrials.gov.[6]
  -- The CLABSI elimination explanation was deleted.

Delayed and Not Reporting of Data: Data for the reporting of Urinary Tract Infection Results was delayed in reporting to Clinical Trials.gov. and the data on Antimicrobial Resistance still has not been reported.

- Urinary Tract Infections.
  -- Anticipated Reporting Date: June, 2015. "Results not yet reported" as of Oct. 16, 2016. [9]

  2015, Dec. Data from REDUCE MRSA study reported in The Lancet Infectious Disease. [10] Previous to this, the protocols for Chlorhexidine use had been widely disseminated and adopted by many hospitals.[11] After the Lancet publication, data was reported on ClinicalTrails.gov.

- Development of Resistance to Mupirocin and Chlorhexidine.

Emergence of Resistance to Mupirocin and Chlorhexidine.
-- Initial anticipated Reporting Date. March, 2015.[9]
-- Reporting date changed To Oct. 2016. "Results not yet reported" as of 12/17/2016.[3]

The emergence of resistance to Mupirocin and Chlorhexidine was also not declared a safety issue on ClinicalTrials.gov.[3]

We feel reduced susceptibility to chlorhexidine is a critical issue. Naparstek, et, al., observed that "Reduced susceptibility to chlorhexidine appeared to be independent of the expression of cepA, acrA and kdeA efflux pumps." "Reduced susceptibility to chlorhexidine may contribute to the success of XDR K. pneumoniae as a nosocomial pathogen, and may provide a selective advantage to the international epidemic strain K. pneumoniae ST258."[12]

In addition, chlorhexidine has been found to promote resistance to last resort antibiotic, Colistin, in K. pneumoniae. This is of grave concern and a subject of a recent publication in Antimicrobial Resistance and Chemotherapy.[13]

Because of the above concerns with the integrity of research and description of results in this manuscript, along with the profound impact this paper has seemed to have had on healthcare policy, we would like to request a review of the study with consideration for possible retraction.

It is not the purpose of this communication to establish the safety or efficacy of chlorhexidine but to express our concern that the REDUCE MRSA study should not be part of the body of evidence to establish standards for its use or inclusion in healthcare policy. We are requesting this inquiry because of this concern.

Thank you for this consideration,

Kevin T. Kavanagh, MD, MS,
Health Watch USA
Somerset, KY

Kathy Day, RN,
Patient Safety Advocate
Bangor, ME

Stephen Tower, MD,
Affiliated Professor WWAMI
Anchorage, AK

Suzan Shinazy, RN,
Patient Safety Advocate
Bakersfield, CA

Martha Deed, Ph.D.
Patient Safety Advocate
North Tonawanda, NY

Rachel Brummert, Executive Director
Quinolone Vigilance Foundation
Charlotte, NC

Julia Hallisy, DDS
The Empowered Patient Coalition
San Francisco, CA

Alan Levine
Patient Advocate
Washington, DC

Linda Radach
Patient Safety Advocate
Lake Forest Park, WA

Alicia Cole
Alliance for Safety Awareness for Patients (ASAP)
Sherman Oaks, CA

David Antoon
Colonel, USAF, Retired
Patient Safety Advocate
Beavercreek, OH

Kim Witczak, Co-founder
Woodymatters
Minneapolis, MN

Yanling Yu, PhD
Washington Advocates for Patient Safety
Seattle, WA

Rex Johnson
Washington Advocates for Patient Safety
Seattle, WA

Joleen Chambers
Failed implant Device Alliance
Dallas, TX

Rose Bartel, BS, MS
Patient Advocate
Chilton, WI, USA

Dan Walter
Patient Advocate
DeLand, FL

Lisa Freeman
Executive Director
Connecticut Center for Patient Safety
Fairfield, CT

Patricia J. Skolnik
Citizens for Patient Safety
Denver, CO

Pat Mastors
Executive Director
Patients' View Institute
East Greenwich, RI

Carol & Ty Moss
Nile's Project MRSA
Perris, CA

CC: Lauren Lindenselser. Editor for Letters Dept.

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