Fluid Management in Acute Respiratory Distress Syndrome: Do We Have All the FACTTs to Determine the Effect of Race?

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In this issue of *AnnalsATS*, Jolley and colleagues (pp. 1443–1449) reexamined the differences in mortality by race and fluid strategy of the 2006 FACTT (Fluids and Catheters Treatment Trial) (1). As a reminder, FACTT used a 2×2 factorial design to randomize patients with acute respiratory distress syndrome (ARDS) to test: (1) a conservative versus a liberal fluid strategy after reversal of shock, and (2) management with a pulmonary artery versus a central venous catheter (2). FACTT demonstrated that a conservative fluid strategy shortened the duration of mechanical ventilation but had no clear effect on 60-day mortality among the entire study population. However, a subgroup analysis demonstrated that black patients had an overall higher mortality than white patients and a trend toward improved mortality with a conservative fluid strategy (2).

In the present study, Jolley and colleagues aimed to further explore if race modifies the effect of fluid strategy on longer-term mortality in patients with ARDS (1). They performed a secondary data analysis of patients enrolled in both FACTT and its follow-up study, the EAPAC (Economic Analysis of Pulmonary Artery Catheters) study (2, 3). To compare mortality at 1 year, the investigators used propensity score matching to balance confounders between black and white patients, and they imputed 1-year mortality for patients without long-term follow-up. With this analysis, the authors demonstrated a significant interaction

($P = 0.012$) between race, fluid strategy, and long-term mortality. Specifically, the authors estimated a significant reduction in 1-year mortality in black patients assigned to conservative compared with liberal fluid management (38 vs. 54%; $P = 0.027$), with similar results after propensity score adjustment. Contrasting these results, fluid management strategy was not associated with mortality in white patients.

Although the results of this study are provocative regarding racial disparities and individualizing care, we agree with the authors' discussion that they are far from conclusive. To take the 10,000-foot view, although this is a skillfully performed study, it is also a secondary analysis of a trial subgroup where nearly one-third of the outcomes were imputed, and the analysis was unable to adjust for many important factors (e.g., socioeconomic) that are known moderators of racial disparities. The authors used a robust statistical methodology to estimate mortality, with their model incorporating information from every patient. Furthermore, the matched propensity score incorporated acute physiologic and chronic comorbidity variables in an attempt to balance confounders among black and white study participants. Finally, they performed a sensitivity analysis that demonstrated it was unlikely that the imputation of missing outcomes data significantly influenced the result.

Methodological issues aside, do the results from the current study provide new insights to change current best practices?

Current best practice already encourages a conservative fluid strategy for many ICU patients and particularly all patients with ARDS who are not in shock or suffering prerenal acute kidney injury (4). The preponderance of clinical data, including FACTT, appears to consistently report that conservative fluid management improves patient outcomes (2, 5–7). Within this line of reasoning, this study does not influence current conservative approaches to fluids in patients with ARDS. However, the authors posit that conservative fluid management may be particularly beneficial in black patients, which would be a novel finding for further exploration. More provocatively, the authors could have posited that fluid management is not relevant in white patients—certainly not a position we would take without clear data to support it.

Are there other explanations to speculate for the difference in estimated effect of fluid management strategy between the two groups? Jolley and colleagues noted greater lack of follow-up in black compared with white patients enrolled in EAPAC (1). Despite results of the sensitivity analysis, this finding, coupled with a lower number of black patients to begin with, may have unpredictable effects on the estimated outcome and its generalizability. In addition, patients in FACTT assigned to a pulmonary artery catheter had more catheter-related complications, especially arrhythmias (8). In the present study, it is unclear if data from black and white patients were matched by type of catheter inserted and whether the long-term

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sequelae of arrhythmias may have affected 1-year mortality.

Examining differential treatment effects by demographic subgroups is essential to eliminating disparities in clinical trials, care, and outcomes. For clinical trials, the Department of Health and Human Services, Food and Drug Administration, and National Institutes of Health all recommend recruiting diverse participants and analyzing for differential outcomes by ethnicity and race (9). The impact of race has been evaluated in a variety of clinical settings, including the intensive care unit (10, 11). Previous literature has demonstrated that in comparison to white patients, black patients have a higher incidence and mortality in ARDS and sepsis (the most common ARDS risk factor) (10–12). In FACTT, the unadjusted 60-day mortality was higher in black compared with white patients in both conservative (31 vs. 24%) and liberal (37 vs. 23%) fluid management arms (2). The results of the present study follow a similar pattern, and the authors speculate on potential genetic explanations for these differences, citing that black patients may have less

renin-angiotensin activation, lower bioavailability of nitric oxide, and increased production of inflammatory cytokines. Although studies have evaluated the genetic associations of ARDS and sepsis according to race (13), the contribution of racial differences in allelic frequencies to disease outcomes is not clearly defined (14). Furthermore, within this theoretical framework it is not evident how any gene product may interact with 7 days of acute fluid treatment to significantly affect mortality at 1 year more than at 60 days. The assignment of differential effects by race to underlying biological causes must be performed with caution (14).

It has been effectively argued that race is a social construct, and that social factors such as socioeconomic status may be the fundamental cause of differential long-term outcomes of individuals suffering the aftermath of a devastating episode of critical illness (15). In the United States, race is associated with socioeconomic status, a fundamental cause of disease disparities that is increasingly recognized to play a role even in the critically ill (12, 16). Although Jolly and colleagues attempted to adjust for

social factors, sociodemographic data were not adequately available to fully estimate their effect on outcomes (1).

In summary, the present study set a new high-water mark for identifying and robustly characterizing the differential response to fluid therapy according to race among patients in the FACTT trial. Our clinical care should continue to focus on lung-protective ventilation and fluid conservative care, and our researchers must further examine the determinants of differential outcomes in critical illnesses. As we do so, we will gain further understanding of the biological and social mechanisms underlying these differences. To clarify the respective genetic and social contributions to outcomes, future studies are needed that identify important subgroups by differences in well-defined biomarkers as well as social determinants of health, such as socioeconomic status, educational achievement, care environment, and social support. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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