The Flaw of Medicine

Addressing Racial and Gender Disparities in Critical Care

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KEYWORDS

• Race • Gender • Health disparities • Minority physicians • Critical care

KEY POINTS

- Race has been identified as an independent risk factor associated with increased morbidity and mortality for some of the leading causes of acute critical illnesses, such as sepsis, acute respiratory distress syndrome, and cardiac arrest. In totality, African Americans have higher death rates than whites for all-cause mortality in all age groups less than 65 years old.
- Racial health disparities involve multiple factors with contributors both on the community and individual ends and within the hospital system itself.
- Gender concordance as well as racial concordance between physicians and patients have been associated with improved outcomes.
- Female physicians and those of minority race remain under-represented in critical care medicine. There is a paucity of systemic data pertaining to reasons behind this disparity, alluding to a need for additional studies targeting the recruitment, training, and retention patterns of the hospital system.

INTRODUCTION

The age of modern medicine has ushered in tremendous advancements and, with them, longevity of life. With early detection of diseases, groundbreaking research

Note: for terminology reasons, use of the sex-specific "male" and "female" in this article are used to differentiate between the 2 most common genotypes XX and XY and not for gender identification.

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leading to curative treatment options for once fatal conditions, and innovative medical devices that serve to all but replace failing organs, there has been a 1.6-fold increase in life expectancy over the past century in the United States.[1] The question is, Has everyone benefited from these developments equally? The presence of gender and racial health disparities suggests that there is work still left to be done. The first target of intervention may well be the medical establishment itself. With research suggesting that patient/physician race and gender concordance results in better outcomes, it becomes imperative to analyze the recruitment, training, retention, and promotion of medical providers reflective of the diverse population that is served.[2,3] The literature presented in this article identifies potential targets for interventions and areas for future exploration. With simple changes, the gap can and will be closed.

PRECISION MEDICINE IN THE INTENSIVE CARE UNIT: INFLUENCE OF BASIC SCIENCE ON HEALTH DISPARITIES

The process of drug development and research to explain pathophysiologic mechanisms prior to the utilization of new medications and modalities for the treatment of patients includes cell cultures, animal models, and different phases of clinical trials.

Classic cell/tissue and animal models use predominately male genotypes. From the perspective of a basic scientist, the all-male animal model assures the most homogenous patient group to explain mechanisms without significant fluctuations in sex hormone levels. Leaving out female cell lines and female animal models completely, however, and assuming that results from an all-male model can be extrapolated to women, is questionable science. The influence of sex hormones on disease and drug interaction at different times during the life span of a woman, including the menstrual cycle, pregnancy, and menopause, is largely unknown and cannot be ignored.

Basic scientists face limitations in choosing the appropriate animal model. For example, it is challenging to model female humans' menopause, when only approximately 4 other mammals (orcas, belugas, short-finned pilot whales, and narwhals) have physiologic menopause.[4] Rodents and other larger mammals do not develop menopause comparable to humans. Therefore, oophorectomy frequently is performed to synthesize a model for postmenopausal patients. Racial and ethnic confounding factors and epigenetic phenomena cannot be modeled with animals either. These only may be simulated, with significant limitations at best.

Hepatic metabolism and renal drug clearance models are based on body weight and muscle mass, which differ between men and women. The possible increased risk of undesirable side effects and drug clearance errors related to different muscle and fatty tissue distribution is substantial when based only on male models.[5] The Food and Drug Administration (FDA) released a safety announcement for zolpidem in 2013, recommending dose adjustment for women to 50% of the recommended dose for male patients, after a significantly higher rate of next-morning cognitive impairment in women compared with men, based on different pharmacokinetics and drug clearance.[6] Other drugs, such as aspirin, utilized for the prevention of myocardial infarction (MI) and stroke, also have been found to vary in their effectiveness and have gender-specific differences in application that need to be taken into consideration.[5]

Clinical trials often still do not allow enrollment of women of childbearing or perimenopausal age. This was routine practice until 1993, when the FDA published a revision of its 1977 guideline, renaming it "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs."[7] This document acknowledges that the exclusion of women of childbearing potential completely leaves out approximately

50% of the population and assumes male sex equals female sex for results. Drugs frequently were approved for both sexes based on this assumption, often with a blanket safety warning for use during pregnancy.

The National Institutes of Health (NIH) Revitalizing Act of 1993 was enacted with the intention to change the practice of study participation. The NIH made it a requirement to include female patients as well as patients of all racial backgrounds represented within the general population in the United States in clinical trials and to analyze subgroups for significant differences as indicated.[7] Although this is a step in the right direction, caution is needed when assuming that results from trials in the United States, which reflect a racial population mix specific to the United States, apply to different racial-ethnic patient populations across Asia, Africa, South/Central America, Australia/Oceania, and Europe. One study result may not fit all.

Sex-specific differences seen in study participation, presentation, and outcome have been noticed in several areas of research, including cancer, traumatic brain injury, Alzheimer disease, and heart disease.[8–11] Variability in outcomes based on ethnic differences has been observed in transplant surgery, cardiac, and pulmonary disease.[12–14] For example, a recent publication by Silva and colleagues[12] highlights the importance of race-match for African American male liver recipients. Although differences in outcomes are noted, the exact pathophysiologic mechanisms of these sex and racial differences are not well understood.

One major improvement in identifying specific genotypes is gene sequencing for so-called single-nucleotide polymorphisms (SNPs), gene loci that help correlate clinical risk factors with specific genetic sequences. This practice is increasingly well known because testing for the breast cancer (BRCA) gene and its mutations/SNPs has led to the option of choosing preventive gynecologic surgeries in high-risk patients. It also is useful in creating chemotherapy protocols based on genetic profiles correlating with optimal drug response patterns. The following studies are all examples of an increasing number of investigations (cell, animal, and clinical) that shed light on sex-specific and race-specific differences. These investigations seek to identify specific genotypes and phenotypes that may be helpful in allowing for an individualized approach and precision medicine in a critical care unit.

Traumatic Brain Injury

Sports-related head injuries, with all severity levels of traumatic brain injury (TBI), have been reported with increasing frequency over the past decade. Consequently, the number of female TBI patients also has increased.[15,16] Most TBI animal models favored male animals. Research with regard to sex-specific outcomes after TBI is a work in progress. The role of sex hormones mostly is unclear, depending on the animal model chosen, as reported in a review of 50 TBI animal models by Rubin and Lipton in 2019.[17] Sex played a role in response to vasopressors to improve cerebral blood flow and, on a molecular level, in the evolution of post-TBI inflammatory response.[17,18]

Thoracic Aortic Surgery with Hypothermic Circulatory Arrest

Female sex is an independent risk factor for worse outcome after complex thoracic aortic surgery. Female patients had higher mortality and risk for postoperative stroke despite a lower incidence of coronary artery disease, better cardiac function, and shorter cross-clamp and total cardiopulmonary bypass times compared with male patients.[19]

Postoperative Delirium and the APOE4 Gene

The APOE4 gene is linked to Alzheimer disease. Female patients positive for APOE4 allele have a higher risk for Alzheimer disease compared with male patients. A longitudinal study published by Schenning and colleagues,[20] in 2019, however, demonstrated that male patients positive for APOE4 present with significantly worse postoperative cognitive decline compared with the overall male-female cohort, despite correction for age and comorbidities.

Race-Matching in Liver Transplants

Hepatocellular carcinoma (HCC), a highly aggressive tumor carrying a mean survival estimate of between 6 months and 20 months, is the most common primary tumor of the liver. Due to the aggressive nature of the disease and the side effects of alternative treatment options, liver transplantation often is utilized as the primary modality of therapy for patients with HCC. A recent study by Silva and colleagues,[12] in 2019, revealed African American liver transplant recipients with HCC had improved overall survival when matched with African American organ donors. This held true even while adjusting for comorbidities and disease characteristics.

Basic science research is fundamental in shaping the practice of modern clinical medicine. There are limitations, however, that need to be considered. Better understanding of how these limitations may contribute to the race-based and gender-based health disparities that exist will be paramount in improving care and closing these gaps.

GENDER IMPACT ON HEALTH DISPARITIES IN CRITICAL CARE

Gender and race have tremendous and wide-ranging impacts on health care delivery, with powerful implications for both health care providers and their patients. For many years, there has been evidence that gender affects, often negatively, the care and outcomes of female patients for a variety of reasons. Perhaps one of the most simplistic (and frustrating) illustrations of this is the dramatic discrepancy between the rates of bystander cardiopulmonary resuscitation (CPR) performed in public places on men (45%) versus women (39%), unfortunately translating into a 29% higher likelihood of survival to hospital discharge for men compared with women.[21]

Extensive work has been done to explore the ways gender has played a role in the world of primary and preventative care. It has been recognized that women more often fail to seek care or are nonadherent to treatment regimens due to cost or lack of resources (childcare, time, and transportation).[22] Women with chronic diseases, such as heart or renal failure, have been observed to receive fewer guideline-based diagnostic procedures, get less-invasive treatments, and be referred later for heart or kidney transplantation and/or dialysis. Women with chronic pain more likely are given sedatives as treatment, whereas men more often are prescribed pain medication, and women with rheumatoid arthritis are much less likely to be sent to see a specialist than are men.[23] But does the same hold true for critically ill patients?

MI is a common cause of critical illness and also is an area where gender effects have been heavily investigated. This most likely is due to the well-recognized differences in susceptibility, presentation, and outcomes between women and men. In general, the rate of MIs is declining in every demographic group except young women. Yet women who experience MI are, once again, more likely to receive less-invasive diagnostic and therapeutic interventions and have a higher mortality rate after their first MI.[23] Furthermore, female gender has long been recognized as an independent predictor of increased morbidity and mortality after coronary artery bypass surgery

and, as such, is included as part of many of the risk-stratification scoring systems used by cardiothoracic surgeons.[24] The reasons behind these differences are complex and likely not generalizable.

To understand the impact of patient gender during critical illness, not only must the differences in patient biology and pathophysiology but also the factors that influence diagnosis and treatment strategies be understood. Do women present differently from men with certain illnesses? Do health care providers assess the severity of illness differently in women versus men, and can this affect intensive care unit (ICU) admission rates? Does gender play a role when patients and their families make decisions about aggressiveness of treatment, and do physicians offer the same interventions in the same way regardless of patient gender? Or are physicians' approaches subtly biased?

In looking at patients with varied forms of critical illness, potentially contradictory results begin to be seen. For example, at least in part because of the effects of sex hormones and the differences in the cytokine and other inflammatory response systems, premenopausal women cared for in the ICU after trauma or with sepsis fare better than their male counterparts. Looking at trauma patients, women develop fewer infections in the ICU, with lower rates of pneumonia and bacteremia.[25,26] These results have fueled research into the manipulation of sex hormones as a potential therapeutic strategy.

The FROG-ICU (French and European Outcome Registry in Intensive Care Unit) study, a trial conducted in France and Belgium and published in early 2019, looked at gender-related outcome differences across a large population of ICU patients and found remarkably similar demographic characteristics, clinical presentations, and illness severity between the 2 groups, with no difference in 28-day or 1-year survival rates.[27]

Although it is clear that gender plays a role in a variety of illnesses, it is difficult to make a compelling case that patient gender influences outcomes in the critically ill in a consistent manner. It is especially challenging to try to tease apart the matrix of factors that may contribute to any trends that may be identified. As women physicians gain a more secure footing in many medical specialties, including critical care medicine, however, researchers increasingly are investigating the other side of the coin. What, if any, differences in patient care can be associated with the gender of the health care provider?

Here again, the research is more robust in the nonacute setting. For example, in primary care environments, female physicians often have more patient-centric communication styles and focus more on both preventative care and psychosocial issues.[28] Elderly patients cared for by female physicians during their hospital admissions have lower mortality and readmission rates.[29]

Recently, the unique contributions of female physicians in the critical care setting were examined in 2 significant studies. A publication in the *Proceedings of the National Academy of Sciences*[3] journal garnered national attention in 2018. Greenwood and colleagues reported improved survival for patients presenting to emergency departments (EDs) with an acute MI when cared for by a female physician compared with a male physician. The impact of this difference was most pronounced for female patients. Of the various combinations, female patients cared for by male physicians were the least likely to survive. And the survival of female patients as a whole was positively correlated with the proportion of female physicians working in the department.[3]

In 2019, Meier and colleagues[30] published a study examining the relationship between physician gender and survival in patients who suffer in-hospital cardiac arrest. This retrospective analysis of more than 1000 cardiac arrests found that female code

leadership was associated with an increased likelihood of achieving return of spontaneous circulation (76.8% vs 71.7%) and an increased rate of survival to discharge (37.3% vs 29.8%). The study also looked at the impact of gender concordance between physician and nursing leadership in codes and found that a female code leader and a female code nurse conferred survival benefit over a male code leader with either a male or female code nurse and over female code leaders paired with male code nurses (although this combination of gender concordance amongst physician and lead nurse during a code was quite rare, occurring only 7% of the time).[30]

Although the data represent complex and likely multifactorial associations, they do suggest a potential patient benefit derived from critical care provided by female physicians. They represent yet another facet of the interplay between gender and medicine. Seen as a whole, these findings implore the health care community to take a closer look at the impact gender has on patients, practices, and providers.

RACE IMPACT ON HEALTH DISPARITIES IN CRITICAL CARE

With regard to health care disparities, the topic cannot be addressed without confrontation of the history of medicine and its intersection with race. Throughout American history, there has been a marked phenomenon of increased mortality for patients of minority status, in particular those of African American lineage. This disparity continues into current times. The present-day age-adjusted death rate for the non-Hispanic black population is 1.2 times greater than for whites and, excluding mortality associated with suicide or unintentional trauma, African Americans have higher age-adjusted death rates for 8 of the 13 leading causes of death.[31]

Holding all things constant, including socioeconomic status, educational level, and access to resources, significant disparity remains for African Americans in conditions, such as infant and maternal mortality, death related to cardiovascular disease, and death related to the most common cancers.[32–34] African American children, in comparison to white children, are 2.2 times more likely to die before their first birthday. African American mothers are approximately 4 times more likely to die in the peripartum period than their white counterparts.[32,35]

Furthermore, contrary to common trends, improved socioeconomic status in the form of increased income level and higher attainment of education is not protective as it pertains to racial inequalities in health outcomes. For instance, an African American infant born to a mother with a doctorate degree is approximately 2 times more likely to die in infancy than a child born to a white mother with an eighth-grade education level.[36,37] This variance from the social determinants model, the association of increasing disparities along racial lines even with higher levels of socioeconomic status, also is noted in studies targeting conditions, such as heart attacks, stroke, and several commonly diagnosed cancers like breast, prostate, and lung cancers.[38]

Due to these findings, tremendous efforts have been geared toward understanding the factors that contribute to this gap in medical outcomes in the community as well as infractions within the medical institution. Through these studies, many factors have been suggested as leading to increased morbidity and mortality along racial lines, including the skewed presence of environmental toxins, food deserts leading to undernutrition and malnutrition, physiologic stressors within minority-populated communities, implicit and explicit racial bias among health care providers, and the inequality of resource utilization and availability within minority communities and the local hospitals serving them.[39–50] The totality of this 2-tier system is implicated not only as a contributor to the higher prevalence of diseases commonly treated within the primary care sector in minority communities (eg, hypertension, diabetes, and

asthma) but also in regard to African Americans having worse outcomes for conditions carrying the highest morbidity and mortality within the critical care arena (eg, sepsis, cardiac arrest, and acute respiratory distress syndrome [ARDS]).[39,44–47,49]

Racial Health Disparities in Regard to Mortality Associated with Acute Critical Illnesses

In the United States, more than 5.7 million patients are admitted to the ICU annually, with an overall associated mortality rate upwards of 10% to 29%, with determinants of death largely age and severity of disease.[51,52] Although advancements have been achieved in earlier recognition and treatment of critical disease processes, there remains high mortality associated with certain diagnoses in the ICU, namely ARDS with 50% mortality, sepsis with upwards of 45% to 60%, and in-hospital versus out-of-hospital cardiac arrest, with 75% versus 88% mortality, respectively.[53–57]

Data also reveal that, although treatment strategies often are heavily protocolized, racial health disparities persist among these conditions, with many studies highlighting treatment bias in health care practice as a potential contributor.[58] Winchester and colleagues (2018)[47] demonstrated increased mortality rate associated with critical troponin levels. African Americans presenting with this finding, however, were statistically less likely to have either a consultation from a cardiologist or cardiac catherization performed during their hospitalization in comparison to white patients with similar presentations. Additional studies reveal African Americans are more likely to have delayed admission to an ICU and altogether are less likely to be admitted to a cardiac care unit in comparison to whites, even after controlling for hospital and insurance plans.[59] Moreover, race has been noted as an independent risk factor associated with delayed cardiac arrest interventions, including defibrillation, conferring higher odds of death for African Americans after both in-hospital and out-of-hospital CPR.[46]

Similar disparities exist for ARDS and sepsis. Although there has been a steady decrease in overall mortality from these processes in recent years, African Americans continue to have higher mortality rates for both in comparison to whites.[44,45,60] Researchers present many factors contributing to these findings. With regard to sepsis, it has been established that delayed resuscitation and treatment of the infectious source results in higher morbidity and mortality.[61,62] This understanding led to the founding of the Surviving Sepsis Campaign in 2004, which resulted in the Surviving Sepsis guidelines, which provide optimal treatment pathways for all patients presenting with sepsis.[63] Despite these efforts, subsequent studies continue to show differences in care delivered to critically ill minority patients. Mayr and colleagues[64] (2010) reported that African Americans diagnosed with community-acquired pneumonia are less likely to receive guideline-concordant antibiotics within the recommended 4 hours from presentation in comparison to whites. This is noteworthy in that pneumonia is the most common source of infection associated with severe sepsis, and severe sepsis is the second leading cause of death in noncoronary ICUs, claiming the lives of more than 200,000 people per year in the United States alone.[51,65,66] An interesting study published recently examined outcomes of septic patients after New York State mandated that management follow established sepsis protocols. As would be expected, protocol completion rates increased and mortality rates declined. A closer look at these results revealed, however, that there was a greater protocol completion rate in white patients (14.0 percentage points) compared with black patients (5.3 percentage points).[67] It appeared that hospitals that took care of a larger proportion of black and minority patients struggled with consistent implementation of performance measures. This study highlights the disparities that exist in the care provided in largely minority versus nonminority hospitals and urges policy makers

to be cognizant of the disparities that might arise. It is imperative to put appropriate measures in place when rolling out new mandates, so that all patients benefit from these efforts.

Additional studies, like that of Pines and colleagues[68] demonstrate African Americans having longer ED boarding times while awaiting ICU admission than white patients. Longer boarding time in the ED is directly associated with increased mortality rate for those admitted to the ICU and carries higher rates of ventilatory-associated pneumonia in trauma patients. Additionally, investigators question whether subtle inequalities in health care providers' interventions, for example, delays in diagnosis or treatment of conditions that cause acute lung injury or noncompliance with recommended low tidal volume ventilatory strategies, may factor into the higher mortality rates seen in African Americans diagnosed with ARDS. These inequalities warrant further investigational studies.[69,70]

Racial Health Disparities: The Role of the Physician

The complexities contributing to the racial health disparities, discussed previously, in the continuum of acute critical illness are vast, encompassing the patient, community, and potentially modifiable practices at the hospital level.[39,49,62,71] As physicians, abilities to influence the former 2 factors may be limited to those of an everyday citizen, but the absolute duty to eradicate the influence of the third factor is mandated in the Hippocratic oath that was pledged. Unfortunately, studies continue to reveal deviations in diagnosing practices as well as treatments offered to critically ill minority patients in comparison to majority patients with similar disease processes, throughout their hospital stays.[41,45–47,50,59,64,68,69,71] More and more, studies are investigating the influence of implicit and explicit biases among physicians and the impact not only on the patient experience but also on morbidity and mortality.[40–43] Physician bias may prove to be the most challenging modifiable risk factor leading to racial health disparities to eliminate.

Race-associated beliefs are developed along the entirety of a life span and become so interwoven in thought processes that recognition of those differences may be subconscious for some, that is, implicit bias.[43] Physicians are no different from the general population in this regard: studies demonstrate equal prevalence of implicit bias among health care providers in comparison to the average citizen, and, alarmingly, but not surprisingly, implicit bias is correlated directly with lower quality of care for targeted patients.[58] Only through the acknowledgment of racial health disparities can a conversation be sparked among physicians and other members of the health care team, allowing for individual and collective reflections and discourse that ultimately will improve the health care systems.

SUMMARY

Disparities exist and affect all facets of medicine. Although gender disparities have historically received more investigative efforts, race and ethnicity have more recently been shown to be integral components woven into the tapestry of disparity. The repercussions of these elements in the care provided for patients have been recognized over time. From the structure of basic science research models, which are the backbone of modern medicine, to the differential care provided to patients based on their gender, racial, and ethnic differences, these disparities are deeply ingrained in medicine. Recognition is the first step in addressing and eliminating the barriers that exist. Through this narrative, these concerns have been attempted to be brought to the forefront, to help physicians move forward from a state of subconscious bias and enable them to provide the best care they can to every patient they see.

DISCLOSURE

E.J. Hilton is a cofounder of a medical consulting firm, GoodStock Consulting, LLC, where the mission is based on addressing racial health disparities.

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