

the 2009 American Reinvestment and Recovery Act, the Institute of Medicine (IOM) was charged with developing a list of CER priorities for the United States (8). For better or worse, critical care medicine was largely overlooked. The irony in many ways is that the critical care community has been a leader in examining the comparative benefit of specific therapies, treatment strategies, and health care structure. There have been numerous studies that examined the comparative efficacy and effectiveness of treatments such as fluid management strategies, hemodynamic monitoring, and mechanical ventilator strategies (13–15). Perhaps stakeholders appreciated the ongoing efforts and felt that less attention was needed for ICU care. However, it is more likely that the critical care (and pulmonary and sleep medicine) community did not adequately promote the importance of their research agenda relative to other potential research areas. When determining how future CER funding will be allocated, the critical care community will likely be at a competitive disadvantage to those whose work falls within the realm of the IOM top 100 priority list. Whether the paucity of critical care topics on the IOM priority list will have reimbursement implications remains to be determined.

CER is one potential methodology to improve the value and efficiency of health care that extends beyond the ICU. Critical care clinicians should be prepared to recognize the potential benefits of CER to patients and health systems as well as the potential effect that it may have on their daily practice. Moreover, as stakeholders prioritize the resources allocated to health care, it will be important for the critical care community to highlight the significant value that they bring for the wellbeing of patients, payers, and policy makers. Health care delivery is at an important juncture, not only in the United States but in other industrialized countries. Dollars devoted to health care are dollars that cannot be used to support other important interests. CER is a tool that may help facilitate the wise spending of these fixed resources.

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Long-acting β -Agonists and Asthma: The Saga Continues

Long-acting β -agonists (LABAs) were originally approved for the treatment of asthma in the early 1990s. Despite nearly 20 years of experience with these medications, there is a storm of controversy about their appropriate place in the treatment of asthma. The article by Wechsler and coworkers in this issue of the *Journal* (pp. 1247–1253) will add yet a new twist to this controversy (1).

To give some historical perspective, LABAs were approved for use in the United States in 1994. At that time, there were clear data showing benefits of LABAs on lung function and other outcomes, but there had been a recent report from the United Kingdom

suggesting an increased risk of death in patients treated with LABAs (2). It was not clear whether patients who had died while taking LABAs had been taking inhaled corticosteroids. Because of this issue, the U.S. Food and Drug Administration (FDA) requested a safety monitoring trial in the United States. Enrollment for the U.S. safety monitoring study opened in 1996 but, as most are aware, was stopped in 2003 because of difficulty with enrollment and asthma-related deaths in participants taking salmeterol. Those deaths appeared to predominate in African Americans (3). Again, there was uncertainty about whether patients who died were actually taking other controller therapy

during the trial. This latter result led to the issuance of a black box warning for LABAs, and to in-depth review of their safety.

A number of studies were published (4, 5), and the FDA undertook a detailed meta-analysis of studies involving LABAs, with and without inhaled corticosteroids (6). The results of the FDA's analyses suggested that adverse events related to LABAs were a concern, but there seemed to be a mitigating effect of inhaled corticosteroids. This was discussed in detail in a joint meeting in December 2008 between the Drug Safety and Risk Management Advisory Committee, Pediatric Advisory Committee, and the Pulmonary-Allergy Drug Advisory Committee (7), and led to the current position in which LABAs are approved as add-on therapy for the treatment of poorly controlled asthma, but should be weaned when asthma is controlled (though there are little data on the safety of weaning LABAs) (8).

Why should LABAs put patients at risk of severe adverse events? No one is certain, though it is well known that overuse of short-acting β -agonists is associated with increased risk of death in asthma, perhaps through blunting of a patient's perception of worsening asthma, and/or simply treating symptoms without treating inflammation. LABAs may have a similar effect. There has also been a great deal of interest in the possible role of genetic polymorphisms in mediating adverse effects of β -agonists, particularly the arg/arg polymorphism at position 16 of the β -adrenoreceptor. Observational studies suggest that this polymorphism is associated with increased risk of adverse outcomes from LABAs (9). A clinical trial evaluating the effects of this polymorphism on lung function in response to LABAs showed no effect on peak flow but was not powered to address the issue of asthma exacerbations (10), and clearly inadequately powered to investigate the effects of this polymorphism on asthma related death (which would require many tens of thousands of patients). Certainly this allele is more common in African Americans, but it is also present in whites (allele frequency 0.5 in African Americans [11], 0.37 in a white Scottish population [9]), so it likely does not explain the whole story regarding adverse effects of LABAs particularly in African Americans.

Now into this controversy steps a publication from the NIH-sponsored Asthma Clinical Research Network (1). This was a retrospective study using pooled data from a number of trials, and there are clear limitations to this form of analysis as acknowledged by the authors. Nevertheless, there were important findings worthy of our immediate attention. African Americans assigned to LABAs had an increased rate of treatment failure regardless of use of other controller medication. To be sure, many of these treatment failures were related simply to increased use of rescue inhaler, but African Americans used less rescue inhaler at baseline. It is also unlikely that the study was powered to see effects on more serious asthma exacerbations. Perhaps this increased use of rescue inhaler could be an early warning signal, the forerunner of more severe events.

Where to put these data in the context of other studies of LABAs? It is another piece of evidence that African Americans may be particularly at risk of adverse events from LABAs. The study also suggests that inhaled corticosteroids and other controller therapy may not be as protective as we had thought in African Americans. Race may be a significant factor in modifying response to therapy. As many of the original studies of LABAs were performed in predominantly white populations, we must recognize the limitations of our knowledge when it comes to effects of medications in other ethnic groups. We must be sure we adequately assess the risk and benefits of therapies in

our individual patients, and be aware that the risk-benefit profile may differ by race. The results of prospective studies evaluating the safety of LABAs in different patient groups are eagerly awaited (12).

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