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Critical Care [ALERT]

Authoritative, evidence-based summaries for the critical care clinician

SPECIAL FEATURE

To Transfuse or Not Transfuse

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Dr. Walter reports no financial relationships relevant to this field of study.

BACKGROUND

In 1818, James Blundell performed the first successful human blood transfusion in a woman with postpartum hemorrhage.[1] Nearly 200 years later, about 15 million red blood cell (RBC) units are transfused annually in the United States.[2] Many of these transfusions occur in the intensive care unit (ICU), where up to 30-50% of patients are transfused.[3-5] Despite the frequency of RBC transfusions, there is little evidence that transfusions benefit patients. There have been no randomized, controlled trials demonstrating that RBC transfusions save lives. The expected benefits from transfusions have largely been extrapolated from very early successes treating massive hemorrhage in obstetric and trauma patients, where transfusions were truly lifesaving.[6] Today, most patients are transfused for anemia, not hemorrhage, and assuming patients today will have the same benefit is overly optimistic.[5]

The primary argument for RBC transfusion is to improve oxygen delivery (DO_2). When oxygen consumption (VO_2) exceeds DO_2, tissue ischemia will develop. DO_2 is the product of cardiac output (CO) and arterial oxygen content (CaO_2):

$$DO_2 = CO \times CaO_2$$

CaO_2 is comprised of oxygen bound to hemoglobin (Hb) and oxygen dissolved in plasma:

$$CaO_2 = (SaO_2 \times Hb \times \text{constant}) + (PaO_2 \times \text{constant})$$

Where SaO_2 is the hemoglobin oxygen saturation, Hb is the hemoglobin concentration, and PaO_2 is the partial pressure of oxygen in arterial blood.[6] Under most circumstances, the amount of oxygen bound to Hb far exceeds the amount of oxygen dissolved in plasma. Therefore, it makes intuitive sense that by increasing a patient's Hb concentration, CaO_2 will increase and in turn DO_2 will increase. However, evidence that improving

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Critical Care [ALERT]

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DO_2 leads to better tissue perfusion and less ischemia is lacking. This is in part because under normal conditions about 4-5 times more oxygen is delivered than consumed, providing a wide margin of safety.[6,7] Even in anemic patients, DO_2 is so much greater than VO_2 that most patients are not at risk for tissue ischemia and may not experience benefit from the additional oxygen carrying capacity provided by additional RBCs.[6]

In addition to a potential lack of benefit, RBC transfusions are costly and have both known and unknown risks. Since the first reports of HIV transmission in 1982, the fear of infection has dominated the discussion of transfusion risks. The first question many patients will ask prior to consenting for a transfusion is what is their risk of contracting HIV or hepatitis. Physicians will often assuage patients' fears by accurately informing them that given today's screening protocols, the risk of viral infection transmitted via RBC transfusion is quite rare. Estimated risks of transfusion-related infection are currently < 1 in 1 million for HIV and hepatitis C and approximately 1 in 350,000 for hepatitis B, on par with the risk of dying in an airplane crash or being killed by lightning.[2] Often not discussed are more common and at times serious transfusion-associated risks. Fever and transfusion-associated cardiac overload occur in about 1-8 out of every 100 transfusions. The risk of transfusion-related acute lung injury is about 1 in 10,000 and life-threatening reactions occur in about 1 in 140,000 transfusions.[2]

Given unproven benefits and potential risks, a number of recent studies have compared "restrictive" and "liberal" transfusion strategies. A restrictive strategy delays transfusion until a lower Hb threshold is reached (usually a Hb of < 7 g/dL). A liberal strategy permits transfusion at a higher Hb threshold (usually a Hb of 9 or 10 g/dL). Several of the more notable transfusion strategy studies will be reviewed here and are summarized in the Table.

TRANSFUSION STRATEGY TRIALS

Of most relevance to ICU physicians was the landmark Transfusion Requirements in Critical Care (TRICC) trial, published in 1999.[8] Hebert and colleagues randomized more than 800 euvolemic ICU patients with a Hb ≤ 9.0 g/dL to a restrictive or liberal transfusion strategy. Patients randomized to the restrictive strategy were transfused only if the Hb was < 7 g/dL, with a goal between 7-9 g/dL. Patients randomized to the liberal strategy were transfused for a Hb < 10 g/dL, with a goal of 10-12 g/dL. Notable exclusions were active blood loss or admission following a routine cardiac surgical procedure. Patients in the restrictive group were transfused on average three red-cell units per patient less than those in the liberal group. Furthermore, 33% of patients in the restrictive group were never transfused compared to 0% of patients in the liberal group.

Death from all causes at 30 days was the primary outcome and occurred less frequently among patients in the restrictive compared to the liberal group (18.7% vs 23.3%, respectively; 95% confidence interval [CI], -0.84 to 10.2%; *P* = 0.11). While this primary outcome did not quite reach statistical significance demonstrating increased mortality with a liberal transfusion strategy, the results strongly suggested no benefit to a liberal transfusion strategy. Furthermore, a restrictive transfusion strategy did significantly reduce the rate of death in two *a priori*-defined subgroups: younger patients (age < 55 years) and patients with lower illness severity (APACHE II score ≤ 20). For patients < 55 years old, mortality was 5.7% in the restrictive group compared to 13% in the liberal group (95% CI, 1.1-13.5%; *P* = 0.028). For patients with lower illness severity, mortality was 8.7% vs 16.1% for the restrictive and liberal groups, respectively (95% CI, 1.0-13.5%; *P* = 0.03). The authors also looked at a third *a priori* subgroup; patients with cardiac disease. Even among patients with cardiac disease, there was no measurable benefit for a more liberal transfusion strategy (30-day mortality

Table. Key Clinical Trials Comparing a Restrictive vs Liberal Red Blood Cell Transfusion Strategy						
Patient population	Hb threshold (g/dL)	Patients transfused (%)	Notable inclusion criteria	Notable exclusion criteria	Primary outcome	Additional information
Intensive care (TRICC)[8]	7 vs 10	67 vs 99	ICU patients age ≥ 16 years who were considered to have euvolemia	Active blood loss or post-op from cardiac surgery	No difference in 30-day all-cause mortality (18.7% vs 23.3%)	30-day all-cause mortality was lower for the subgroups of patients with APACHE II score ≤ 20 and patients < 55 years
Cardiothoracic surgery (TRACS)[9]	8 vs 10	47 vs 78	Patients ≥ 18 years undergoing elective CABG or valve replacement surgery	Aortic procedures, preoperative Hb < 10 g/dL	No difference in composite outcome of 30-day all-cause mortality or severe comorbidity (11% vs 10%)	Number of transfused RBC units was an independent risk factor for clinical complications
Post hip fracture repair (FOCUS)[10]	8 vs 10	41 vs 97	Age ≥ 50 years undergoing hip fracture repair with clinical evidence or risk factors for cardiovascular disease	Acute MI within 30 days, symptoms of anemia, or active bleeding	No difference in composite outcome of death or inability to walk without human assistance at day 60 (34.7% vs 35.2%)	No difference in 60-day all-cause mortality (6.6% vs 7.6%)
Acute upper GI bleeding[11]	7 vs 9	49 vs 86	Age > 18 years with hematemesis, melena, or both	Massive exsanguinating bleeding, acute coronary syndrome, stroke, lower GI bleeding	45-day all-cause mortality was significantly lower in the restrictive strategy group (5% vs 9%)	Risk of death was reduced among both patients with and without portal hypertension

Abbreviations: ICU = intensive care unit; APACHE = Acute physiology and chronic health evaluation; CABG = coronary artery bypass grafting; Hb = hemoglobin; RBC = red blood cell; MI = myocardial infarction; GI = gastrointestinal

was 20.5% in the restrictive group vs 22.9% in the liberal group). The authors concluded that among critically ill patients, a threshold for RBC transfusion of 7 g/dL was as effective, and possibly superior, to a threshold of 10 g/dL.

Criticisms of this trial have been that transfused blood was not leukocyte reduced, as is now commonplace. The presence of leukocytes may have led to a more inflammatory reaction in transfused patients and may have explained some differences in outcomes. Additionally, despite the fact that no differences in outcome were seen among patients with cardiac disease, there may have been selection bias as few patients with cardiac disease were enrolled. Finally, only patients who were euvolemic and not actively bleeding were enrolled.

Following the TRICC trial, two subsequent trials addressed the lingering question of transfusion strategies in patients with cardiac disease. The Transfusion Requirements After Cardiac Surgery (TRACS) trial was published in 2010.[9] The trial enrolled 502 consecutive patients following coronary artery bypass grafting or cardiac valve surgery with cardiopulmonary bypass. Patients were randomized to either a restrictive (to maintain a hematocrit of ≥ 24%) or liberal (hematocrit ≥ 30%) transfusion strategy. Similar to the TRICC trial, patients in the restrictive group received fewer blood transfusions. There was no difference in the composite endpoint of 30-day mortality and severe comorbidity (cardiogenic shock, acute respiratory distress syndrome, or acute renal failure requiring dialysis or hemofiltration) between groups (11% restrictive vs 10% liberal; $P = 0.85$).

The following year, the FOCUS trial was published.[10] FOCUS compared a restrictive and liberal transfusion strategy in just over 2000 patients age ≥ 50 years with clinical evidence or risk factors for cardiovascular disease who had undergone surgery to repair a hip fracture. Patients were not critically ill, but they were a high-risk population with a mean age of 81 years. The transfusion trigger for the restrictive group was "symptoms of anemia or at physician discretion for a Hb < 8 g/dL" vs a Hb < 10 g/dL for the liberal group. Once again, a restrictive transfusion strategy was equivalent to a liberal strategy with no difference in the primary outcome of death or mobility at 60 days (35.2% restrictive vs 34.7% liberal; $P = 0.90$).

A trial published in early 2013 addressed transfusion strategies in patients with severe acute upper gastrointestinal bleeding.[11] Patients were randomized to either a transfusion trigger of Hb < 7 g/dL (restrictive) or Hb < 9 g/dL (liberal). Nearly half of the patients (49%) had peptic ulcer bleeding, 31% had cirrhosis, and 21% had esophageal varices. Thirty percent of patients had signs of hypovolemic shock (systolic blood pressure < 100 and heart rate > 100). All patients were transfused leukocyte-reduced RBCs. Remarkably, a restrictive transfusion strategy was associated with a 45% relative-risk reduction in death at 45 days (95% CI, 0.33-0.92; $P = 0.02$). Patients in the restrictive-strategy group also had less rebleeding, transfusion reactions, pulmonary edema, and a shorter hospital length of stay. The decrease in risk of death was primarily due to a decrease in deaths from bleeding that could not be successfully controlled.

The authors suggested that transfusions may counteract normal hypovolemia-induced splanchnic vasoconstriction leading to an increase in blood flow that may impair clot formation.[11] Transfusion may also cause abnormalities in coagulation properties. These results are compelling and coupled with previous trials, strongly argue for a restrictive RBC transfusion strategy in most patients, even in the setting of acute bleeding. However, it is important to note some limitations of this study. Patients with "massive exsanguinating bleeding" were excluded. Moreover, all patients had emergency gastrostomy within 6 hours. In settings where this is not possible, bleeding control may take longer to obtain and results could be different. Furthermore, outcomes among patients with more severe shock were not described. The accompanying editorial recommended that while most patients with upper gastrointestinal bleeding, with or without portal hypertension, should only be transfused for a Hb < 7 g/dL, it is probably reasonable to transfuse patients with marked hypotension at higher Hb levels.[12]

CONCLUSION

Too often, critical care practitioners have been faced with apparent practice-changing studies only to find that results are not replicated in subsequent studies — stress-dose steroids and tight insulin control come to mind. In contrast, with respect to transfusion strategies, repeated studies in different populations have consistently shown the same direction of effect and conclusions: restrictive transfusion strategies are either no worse, and probably superior, to liberal strategies. In addition to the studies reviewed here, similar results have been seen in patients with moderate-to-severe head injury[13] and in several pediatric populations.[14] These data have been accepted by numerous professional societies worldwide, and a restrictive RBC transfusion strategy is supported by many published clinical guidelines worldwide.[2,3,6,7] While there are slight variations, most guidelines recommend a transfusion threshold of Hb of 7 g/dL for most critically ill patients. A threshold of 7 g/dL should also be used in most patients presenting with acute upper gastrointestinal bleeding. In patients with cardiac disease, a threshold of Hb of 8 g/dL may be reasonable, especially if there are signs of anemia.

Of course, clinical decision making needs to be applied whenever RBC transfusions are being considered. A Hb concentration by itself should never be used as the sole determinant of when to transfuse. However, when clinicians are considering transfusion, the benefits of a restrictive transfusion strategy should not be overlooked. Fewer transfusions equate to less cost, fewer patients exposed to the potential harms of RBC transfusion, and potentially decreased morbidity and mortality. ■

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ABSTRACT & COMMENTARY

Reducing Antibiotic Overuse: An Intervention with Positive Outcomes

By Leslie A. Hoffman, RN, PhD

Professor Emeritus, Nursing and Clinical & Translational Science, University of Pittsburgh

SYNOPSIS: Active, daily communication between infectious disease and critical care practitioners significantly reduced antibiotic overuse without increasing mortality.

SOURCE: Rimawi RH, et al. Impact of regular collaboration between infectious diseases and critical care practitioners on antimicrobial utilization and patient outcome. *Crit Care Med* 2013;41:2099-2107.

This study was undertaken to test the potential that routine daily assessment of antibiotic use by an infectious disease (ID) specialist (fellow) could further improve best practices for ICU patients. At the time the study was instituted, the institution had implemented an antimicrobial stewardship program and rounds included pharmacist consultation. However, chart reviews indicated "considerable opportunity" for improvement. Baseline data were collected during a 3-month preintervention period followed by the 3-month intervention that was scheduled 1 year after baseline data collection to avoid seasonal discrepancy. The ID fellow reviewed charts of all medical ICU (MICU) patients receiving antibiotic therapy, discussed complex cases with the ID attending, and rounded with the critical care team to provide recommendations. Antibiotic use was recorded as days of therapy. In this calculation, each antibiotic given on a single day was recorded as 1 day of therapy (DOT), i.e., 1 antibiotic/day = 1 DOT and 3 antibiotics/day = 3 DOT. DOTs were divided by length of stay (LOS); the ratio was multiplied by 1000 and expressed as DOT/1000 patient days to allow comparison between cohorts with differing LOS. Antibiotics given prior to MICU admission or after MICU discharge were not included.

A total of 246 charts were reviewed: 123 in the preintervention phase and 123 in the post-intervention phase. There were no significant between-group differences in age, gender, race, APACHE II scores, or types of infections. Fewer patients received antibiotics that did not correspond to guidelines during the intervention period ($P < 0.0001$). There was a significant reduction in antibiotic use during the intervention period (1590 vs 1420 DOT/1000 patient days; $P = 0.03274$). There was also a 17-fold increase in the use of narrow-spectrum penicillins (e.g., penicillin G and nafcillin) in the intervention phase (67 vs 4 DOT/1000 patient days; $P = 0.0322$). All-cause hospital mortality was significantly lower in the intervention phase ($P = 0.0367$) with no difference in all-cause MICU mortality ($P = 0.4970$). There was a significant reduction in days of mechanical ventilation (6.07 vs 10.1; $P = 0.0053$) and MICU LOS (7.78 vs 10.29; $P = 0.0188$) in the intervention period, compared to the preintervention period. Cost of antibiotics in the preintervention period exceeded that in the intervention period by a difference of $22,486.

■ COMMENTARY

Efforts to better match antibiotic prescriptions with patient needs are clearly warranted. In this institution, an antibiotic stewardship program had already been instituted. However, despite existence of this program and the inclusion of a pharmacist on rounds, there continued to be a need for improvement, based on chart reviews. The ID specialist made 180 recommendations during the 3-month course of the study. Specific recommendations related to shortening (n = 77), stopping (n = 53), narrowing (n = 34), or broadening therapy (n = 4), as well as converting to oral administration (n = 8) and changing therapy due to an adverse effect (n = 4). Thus, most (72%) recommendations related to more timely cessation of therapy.

The authors posed several reasons for this outcome. Rather than lack of knowledge, they suggested that reluctance to change therapy was potentially related to hesitation to abruptly change antibiotics after a handoff of care, even when there was awareness that a change was indicated, until familiar with the case. Because the ID specialist was actively involved in discussions during MICU rounds, there could be "consensus discussions" leading to change. When proposing the intervention, there was concern that disputes might arise between specialties. This did not occur and the volume of ID consultations was not affected.

When calculating cost saving, the analysis only considered hospital pharmaceutical acquisition costs. No costs were attributed to the ID specialist, who was a fellow, since the experience was considered part of training. The time requirement for providing consultation (estimated at 2 hours/day) was not excessive and the experience was judged an excellent academic fellowship opportunity. The study, therefore, met its goal of achieving better antibiotic stewardship with no untoward consequences. The benefits of an ID specialist participating in rounds on patients with sepsis on clinical units have been well documented. The current study extends these benefits to the ICU setting. ■

ABSTRACT & COMMENTARY

Effects of ICU Capacity Strain on Patient Outcomes and ICU Discharge Timing

By David J. Pierson, MD, Editor

SYNOPSIS: Data from 155 ICUs over an 8-year period showed that patients admitted on days with ICU capacity strain (high census, new admissions, and/or higher patient acuity) experienced higher in-hospital mortality. However, unit strain on the day of ICU discharge was associated with fewer hours in the ICU and a slightly increased likelihood of ICU readmission, but there was no adverse effect on any patient outcome examined.

SOURCES: Gabler NB, et al. Mortality among patients admitted to strained intensive care units. *Am J Respir Crit Care Med* 2013;188:800-806. Wagner J, et al. Outcomes among patients discharged from busy intensive care units. *Ann Intern Med* 2013;159:447-455.

Two studies by the same group of investigators, published simultaneously in different journals, used a large nationwide database (the Cerner Corporation's Project IMPACT) to examine the influence of ICU capacity strain (that is, ICU census, new admissions, and average patient acuity) on patient outcomes. Project IMPACT includes data from 155 ICUs in the United States, and is considered to be representative of critical care in this country: 73% of its units are in community hospitals and 58% are in urban centers. The data used for these retrospective cohort studies came from patients cared for from 2001-2008, a period when a closed model for daytime intensivist staffing was in effect in 7% of the participating ICUs.

Gabler and colleagues sought to determine whether transient increases in ICU strain, present on the day a patient is admitted to the unit, influence in-hospital mortality. Their study population consisted of 264,401 patients, of whom 36,465 (14%) died in the hospital. By several measures of how busy the unit was at the time, being admitted at a time of increased ICU capacity strain was associated with an increased likelihood of dying in the hospital. This association was greater in ICUs with a closed physician staffing model: odds ratio (OR) 1.07; 95% confidence interval, 1.01-1.11 for closed units, vs OR 1.01 (95% CI, 0.99-1.03) for open units (P = 0.02). These findings persisted despite several statistical procedures for reducing the effects of confounding variables.

To test the hypothesis that ICU capacity strain may result in patients being moved out of the ICU too soon, with adverse consequences, Wagner et al examined the same three aspects of ICU strain (ICU census, new admissions, and average acuity), assessed on the day of ICU discharge, in relation to ICU length of stay and post-ICU discharge outcomes. Their study population, from the same 2001-2008 Project IMPACT database used by Gabler et al, consisted of 200,730 patients discharged from the 155 ICUs to hospital floors. In these patients, they sought to determine associations between ICU capacity strain metrics and ICU length of stay, 72-hour ICU readmissions, subsequent in-hospital death, post-ICU discharge length of stay, and hospital discharge destination. Examination of the data included multiple adjustments for patient characteristics and severity of illness, as well as for whether they had received mechanical ventilation or vasoactive infusions during their ICU stay.

Of the 200,730 patients who survived their ICU stay and were discharged to a hospital floor or step-down unit, 3% were readmitted to the ICU within 72 hours, 4% died in the hospital, and 63% were discharged from the hospital to their homes. Increases in the three measures of ICU strain were associated with shorter preceding ICU length of stay ($P < 0.001$ for each), and increased likelihood of ICU readmission (all, $P < 0.05$). The magnitude of the former effect was numerically small but statistically significant: increases in all strain variables from the 5th to the 95th percentiles of the data distributions resulted in a mean decrease in expected ICU length of stay of 6.3 hours (CI, 5.3-7.3 hours). However, no strain variable was associated with increased odds of subsequent death, decreased likelihood of being discharged home, or longer total hospital length of stay.

The authors interpret their findings as indicating that although patients tend to be moved out of the ICU more quickly when the unit is strained by admissions, census, and/or acuity, and this slightly increases the likelihood of ICU readmission, there are no adverse effects on patient outcomes. One implication of this is that shortening ICU stays in the manner observed in this study — although by little in terms of hours per patient — could have an important effect nationwide in increasing critical care capacity as demands for this resource continue to increase.

■ COMMENTARY

The associations between ICU strain and patient outcomes in these studies are statistically strong but small in magnitude. However, as pointed out by Gabler et al in their discussion, "Small changes in mortality risk, when estimated precisely (i.e., with narrow confidence intervals) as in this study, may have a large cumulative impact and may be important to ICU patients and providers."

The fact that the increase in mortality observed during times of ICU capacity strain was greater for units with a "closed" model for physician staffing than for "open" units deserves comment. Granted, only 7% of the ICUs in the database were closed during the period covered by the study. However, the sample included more than 19,000 patients admitted to closed units. One might think that such units would be more likely to be situated in academic hospitals that manage sicker patients and have a higher proportion of emergently admitted patients, exacerbating the unit strain. However, there is no indication that this was the case, and Gabler et al performed multiple procedures to eliminate such confounders. The authors' explanation, which seems plausible to me, is that closed units may be less flexible than open units in terms of physician staffing at times of short-term surges in census, new admissions, and acuity. Closed units have been shown to produce better patient outcomes under static conditions, but it may be that it is easier to accommodate increased demands for physicians when things get busy in an open-unit environment. This finding deserves further examination. ■

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CME/CNE Questions

1. The primary argument for red blood cell transfusions is to:

a. increase the oncotic intravascular pressure.
b. increase the oxygen carrying capacity of blood.
c. decrease oxygen consumption at the tissue level.
d. increase the partial pressure of oxygen.
e. decrease work of breathing.

2. Under normal physiologic conditions:

a. oxygen delivery is about 4 to 5 times greater than oxygen consumption.
b. increasing the hemoglobin concentration via red blood cell transfusion will increase the oxygen carrying capacity of blood.
c. oxygen delivery is determined by cardiac output and arterial oxygen content.
d. the amount of oxygen bound to hemoglobin far exceeds the amount of oxygen dissolved in plasma.
e. All of the above

3. In an institution with a pre-existing antibiotic stewardship program and ICU rounding pharmacist, the addition of recommendations from an infectious disease (ID) specialist:

a. failed to further improve patient outcomes.
b. led to conflicting recommendations from the pharmacist and ID specialist.
c. reduced antibiotic costs with no change in all-cause ICU mortality.
d. reduced antibiotic costs with no change in all-cause hospital mortality.
e. changed the choice of antibiotics but not the duration of coverage.

4. Which of the following statements is *false* about the study of the effects of daily infectious disease specialist input to antibiotic use in the ICU?

a. Daily ID specialist input reduced inappropriate antibiotic usage.
b. The use of narrower-spectrum penicillins increased.
c. The ID specialist spent 2 hours a day involved in this activity.
d. The cost of the ID specialist's involvement was included in the result calculations.
e. None of the above

5. Which of the following are measures of ICU capacity strain?

a. ICU census
b. New admissions
c. Patient acuity
d. All of the above
e. None of the above

6. Which of the following statements is true about the effects of ICU capacity strain on the day a patient is admitted to the unit with respect to outcomes?

a. Increased ICU strain was associated with an overall increase in patient mortality.
b. Increased ICU strain increased in-hospital mortality in open but not closed ICUs.
c. More strain on the day of ICU admission tended to shorten the length of ICU stay.
d. ICU admission under conditions of increased unit strain increased the likelihood that a patient would be discharged to an extended-care facility.
e. None of the above

CME/CNE Objectives

Upon completion of this educational activity, participants should be able to:

- identify the particular clinical, legal, or scientific issues related to critical care;
- describe how those issues affect physicians, nurses, health care workers, hospitals, or the health care industry; and
- cite solutions to the problems associated with those issues.