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Point-of-Care Testing at the Disaster-Emergency-Critical Care Interface

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Abstract

Point-of-care (POC) testing allows for medical testing to be performed across the disaster-emergency-critical care continuum. The disaster-emergency-critical care continuum begins with the identification of at-risk patients, followed by patient stabilization, and ultimately transfer to an alternate care facility or mobile hospital for comprehensive critical care. Gaps at the interfaces for each of these settings leads to excess mortality and morbidity. Disaster victims are at risk for acute myocardial infarctions, acute kidney injury (AKI), and sepsis. However cardiac biomarker testing, renal function testing, and multiplex rapid pathogen detection are often unavailable or inadequate during disasters. Cardiac biomarker reagents require refrigeration; traditional renal function tests (i.e., serum creatinine) exhibit poor sensitivity for predicting AKI in critically ill patients, and culture-based pathogen detection is too slow to help initiate early-directed antimicrobial therapy. We propose three value propositions detailing how rapid, POC, and environmentally hardened cardiac biomarker, AKI and multiplex pathogen testing harmonizes the interface between disaster, emergency, and critical care.

Keywords

Acute kidney injury; acute myocardial infarction; biomarker; cardiac biomarker; crush injury; neutrophil gelatinase associated lipocalin; pathogen detection; robustness; sepsis; turnaround time

INTRODUCTION

Recent crises highlight both the need and limitation of portable medical testing in disasters.[1] The Asian Tsunami of 2004 and Hurricane Katrina in 2005 showed healthcare facilities being quickly overwhelmed by the massive influx of patients. The movement of patients from disaster zones to nearby healthcare facilities and mobile hospitals may be impaired by damaged or inadequate transportation infrastructure. Advanced hospital diagnostic technologies are rendered useless by loss of electrical power—causing healthcare providers to rely manual on methods for triage and diagnosis until disaster responders arrive and alternate care facilities (ACF) are activated.[1,2]

Point-of-care (POC) testing is defined as medical testing at or near the site of patient care.[3] The use of POC testing for disaster response has seen widespread use in recent events[1] including the combined 2011 Earthquake/Tsunami disaster in Japan and the 2010 Haitian Earthquake.[3,4] Point-of-care testing provides disaster responders with basic imaging (e.g., ultrasound), whole-blood analysis (e.g., electrolytes, metabolites), and vitals monitoring

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capabilities.[1,2] These mobile devices allow medical testing to be performed across the disaster-emergency-critical care continuum.

ESTABLISHING A DISASTER-EMERGENCY-CRITICAL CARE CONTINUUM

We define the disaster-emergency-critical care continuum as the process beginning with the identification of at-risk patients in the disaster setting, followed by stabilization of these patients, and transfer to an ACF or mobile hospital for comprehensive critical care. The lack of key medical testing technology at the interfaces between disaster, emergency, and critical care represent technology gaps that contributes to excess mortality and morbidity.

Disaster-related diseases are often acute in nature, with the most serious requiring immediate triage to emergency and critical care facilities. Chronic diseases are also present and may be compounded by the lack of medical facilities.[1] The use of POC testing accelerates triage, but more importantly, facilitates evidence-based practices necessary for the disaster-emergency-critical care continuum. However, disaster response teams are only equipped with a limited spectrum of POC testing devices consisting of glucose meters, portable ultrasound, and handheld chemistry analyzers.[1,2] Cardiac biomarker testing, acute kidney injury (AKI) detection, and multiplex rapid pathogen identification are often unavailable.

Studies report the incidence of acute myocardial infarction (AMI) being significantly higher following emotional stress as encountered in disasters.[5] However, Disaster Medical Assistance Teams (DMAT) deployed to Hurricane Katrina in 2005 reported the lack of cardiac biomarker tests due to refrigeration requirements preventing pre-stockpiling of reagents.[1,6] These responders must rely on patient history, physical examination, and electrocardiograms to rule-in/rule-out AMI. Point-of-care cardiac biomarker testing is recommended in these pre-hospital settings to help improve outcomes.[7]

Acute kidney injury is defined as the sudden loss of renal function[8] and may occur in disasters following trauma such as crush injury.[9] Crush injuries in disasters have been reported as recently as the 2011 ChristChurch Earthquake in New Zealand[10], and can progress quickly to severe AKI. The management of crush injuries requires rapid renal function testing to determine risk for AKI and provide life-saving interventions to preserve or restore renal function. Serum creatinine can be performed at the point of care; however, creatinine measurements may become unreliable in the critically ill.[11,12] Novel POC biomarkers are needed to help rule-out AKI following crush injury.

Pathogen detection is also limited in disaster settings. Disaster Medical Assistance Teams are equipped with rapid swab-based immunological assays for detecting influenza and *Streptococcus* pharyngitis.[6] Gram's stain and microscopy are available, however, do not facilitate definitive treatment (e.g., pathogen speciation and antimicrobial drug susceptibility) and is not compatible with early goal directed therapy initiatives designed to reduce the mortality associated with severe infections like sepsis.[13–15] Clinical needs assessment surveys conducted by the University of California, Davis POC Technologies Center revealed the need for bloodstream and respiratory infection detection in disaster settings—emphasizing the critical need for rapid pathogen detection during crises.[16,17]

We propose three value propositions emphasizing the potential benefits associated with POC testing at the interface between disaster, emergency, and critical care.

VALUE PROPOSITIONS

Cardiac Biomarker Testing

Problem—Acute myocardial infarctions occur frequently following disasters during the dynamic response phase.[17–19] Leor et al. reported a modest, yet significant increase (35%, from 149 to 201, P = 0.01) in the number of emergency department admissions for AMI immediately after the 1994 California Northridge Earthquake.[20] Interestingly, hospitals located ≤15 miles from the Earthquake epicenter had significantly (P = 0.01) higher AMI admissions compared to those located ≥15 miles. Similar observations were reported following the 1995 Great Hanshin-Awaji earthquake in Japan.[21] In the end, delays in recognizing AMI adversely affected outcomes.[22]

Disaster response teams are poised to identify AMI early and quickly initiate appropriate interventions. Highly sensitive quantitative cardiac biomarker assays and serial testing help rule-out AMI.[22] Point-of-care cardiac biomarker testing accelerates therapeutic turnaround time and makes serial testing feasible. Despite convenience, POC cardiac biomarker tests require refrigeration[23,24]—limiting their ability to be pre-stockpiled for use in disaster environments.

Value Hypothesis—Robust POC cardiac biomarker testing provides early patient recognition, risk stratification, and serial testing for AMI's through the disaster, emergency, and critical care continuum.

Solution—Development of environmentally robust POC assays and/or thermomodulating containers to protect reagents against extreme testing conditions allows cardiac biomarker tests to transcend the laboratory environment and expand to high impact disaster, emergency, and critical care settings.

Evidence—The use of cardiac POC testing in pre-hospital (e.g., aeromedical transport, disaster, and field settings) settings allows for early risk stratification and improved outcomes.[25–28] Investigators using qualitative and highly sensitive POC cardiac troponin T tests in pre-hospital settings identified more patients with AMI than using 12-lead electrocardiogram changes alone.[29]

Robust medical testing devices and equipment are commonly used by the military.[1] Military responders are equipped with mobile, solid state, thermomodulating containers to maintain adequate storage conditions for POC reagents including cardiac biomarker assays and handheld chemistry analyzers.[1,30] Additionally, the United States Army Medical Research and Material Command (USAMRMC) is in the process of developing a cardiac biomarker assay for AMI using an environmentally robust test platform.[31]

Point-of-Care Determination of Acute Kidney Injury Following Crush Injury

Problem—The incidence of acute kidney injury (AKI) has increased from 60 to 500 events per 100,000 patients over the last decade.[32,33] Based on the Risk, Injury, Failure, Loss, and End-Stage (RIFLE) criteria for assessing AKI severity[8], investigators have reported a mortality of 18.9, 36.1, and 46.5% in Risk, Injury, and Failure classes respectively.[34,35] Crush injuries in disasters places patients at risk for AKI. The development of AKI is the second most common cause of death after large earthquakes and other natural disasters.[9] Serum creatinine measurements and urine output are common methods for assessing renal function and determining AKI severity in the critically ill.[11,12] Although convenient, urine output is a poor indicator of kidney perfusion; while, serum creatinine has significant inter-patient variability and exhibits poor sensitivity for ruling out AKI in the critically ill.

Value Hypothesis—Point-of-care biomarker testing helps rule-out crush injury-related AKI sustained during disasters and improves the emergency-critical care management of renal dysfunction.

Solution—Neutrophil gelatinase associated lipocalin (NGAL) is a novel and specific biomarker for AKI.[9] During AKI, NGAL concentrations increase in both the bloodstream and urine due to reduce renal elimination and concurrent release of the molecule from epithelial cells found in the nephron. Combined with B-type natriuretic peptide, NGAL may better predict AKI during crush injury.[36]

Evidence—Levels of NGAL in 2 mudslide victims in Messina, Italy enabled early diagnosis of AKI and anticipation of changes in serum creatinine.[9] The performance of NGAL in predicting AKI is enhanced by coupling the biomarker with BNP.[36] Elevated combined BNP/NGAL measurements are highly predictive for AKI and exhibits significantly better performance as compared to serum creatinine. BNP and NGAL levels >267 pg/mL and >231 ng/mL respectively exhibited a hazard ratio (HR) of 10.82 for AKI (95% CI 1.22 to 96.23, P = 0.03), whereas, serum creatinine measurements was less predictive for AKI with HR of 1.00 (95% CI 1.00 to 1.01, P = 0.02).[36]

Rapid Multiplex Point-of-care Pathogen Detection

Problem—Severe sepsis mortality ranges from 28 to 50%.[37] Mortality approaches 80% in cases of septic shock. *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* infections are common following disasters.[16,17] Every hour delay in initiating appropriate antimicrobial therapy in severe sepsis is associated with a 12.7% decrease in survival.[38] Existing hospital pathogen detection technologies such as culture are not suitable for disasters. Culture turnaround times are incompatible with early goal directed therapy sepsis initiatives[13] used in emergency and critical care settings[15]. Rapid swab-based immunoassays and microscopy used by disaster responders lack the clinical sensitivity/specificity, and turnaround time necessary for pathogen detection during sepsis. Consequently, empiric combination antimicrobial therapy is recommended due to the lack of rapid pathogen identification.[15] Although high-risk patients (i.e., septic shock) may benefit from combination empiric therapy, recent meta-analyses suggest that this may be detrimental to low-risk patients (i.e., early sepsis, or sepsis without hypotension) due to possible drug-related toxicity and antagonism.[39]

Value Hypothesis—Rapid multiplex POC pathogen detection improves patient outcomes by facilitating early-targeted antimicrobial therapy in septic patients in disaster, emergency, and critical care settings

Solution—Point-of-care polymerase chain reaction (PCR) and other molecular methods allow rapid pathogen detection to be used in disasters to initiate early-targeted anti-infective therapy while in the field. Current PCR tests exhibit turnaround times of 1 to 6 hours. Modern PCR tests can identify multiple pathogens simultaneously from wound and whole-blood samples.[13] Near patient PCR-based assays are now available and several POC systems are currently under development for testing in field, ACF, mobile hospital, emergency, and critical care settings.

Evidence—Early appropriate antimicrobial treatment exerts a greater effect on improving outcomes irrespective of the pathogen species and source of sepsis.[40] Prospective observational trials evaluating the clinical utility of multiplex whole-blood PCR-based pathogen detection reported test turnaround times ranging from 5.21 to 6.22 hours.[14] PCR testing for skin and soft tissue infections exhibit turnaround times of about one hour.[13] Near-

patient PCR-based pathogen detection systems utilize easy to use and self-contained test cartridges suitable for field, ACF, mobile hospital, emergency, and critical care applications.

CONCLUSIONS

Pre-hospital recognition of AMI, AKI, or sepsis helps initiate early-directed therapy. Thermally robust and environmentally protected POC cardiac biomarker testing allows for AMI detection in austere settings and facilitates serial testing for risk stratification following field triage. Point-of-care NGAL testing allows for early recognition of AKI following crush injury. Multiplex molecular pathogen detection at the point of care helps clinicians and first responders to rapidly identify the microorganism causing sepsis and prompts early initiation of appropriate antimicrobial therapy. Point-of-care testing serves to harmonize the interface between disaster, emergency, and critical care. The implementation of POC cardiac biomarker, AKI, and multiplex pathogen testing addresses significant gaps in the disaster, emergency, and critical care continuum.

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