



Brief Communication

Pancreatitis associated anxiety, depression, and stress: Hypothesis, definition, and intervention

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ABSTRACT

Necrotizing pancreatitis is characterized by a prolonged disease course requiring frequent hospitalization and intervention. Necrotizing pancreatitis patients have high rates of intensive care unit admission and organ failure. Critical illness is an identified risk factor for the development of anxiety, depression, and posttraumatic stress disorder. Limited literature examines quality of life in necrotizing pancreatitis patients, and studies examining psychiatric sequelae of necrotizing pancreatitis including depression, anxiety, and posttraumatic stress disorder are virtually nonexistent. Here, we review critical literature examining risk factors for poor mental health outcomes during and after necrotizing pancreatitis, identify several screening instruments to quantify mental health outcomes, and propose an intervention to improve mental health outcomes in patients with necrotizing pancreatitis. We conclude that establishing the incidence of mental health disorders and implementing strategies to improve mental health outcomes are critical to holistic care of necrotizing pancreatitis patients.

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INTRODUCTION

Necrotizing pancreatitis (NP) affects 15%–20% of the 300,000 Americans diagnosed yearly with acute pancreatitis (AP) [1]. NP is characterized by a prolonged and severe disease course, necessitating frequent intensive care unit admission, multiple readmissions, and numerous interventions. Invasive intervention is frequently required even after NP disease resolution [2], underscoring the long-term nature of this disease.

Severe illness and intensive care unit (ICU) stay are established risk factors for the development of anxiety, depression, and posttraumatic stress disorder (PTSD) [3,4]. In our own high-volume clinical practice, we have observed that mental health frequently deteriorates during both the acute and long-term stages of severe pancreatitis. However, despite significant overlap between NP disease course and critical illness more broadly, the psychologic impact of NP remains dramatically understudied. Furthermore, therapies designed to improve mental health in this population are nonexistent.

The General Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and PTSD Checklist for DSM-V (PCL-5) are established, validated screening tools for anxiety, depression, and

PTSD [5–7]. Each screening tool consists of a series of questions pertaining to the symptoms of each disorder and can be completed by patients in a short time. Mindfulness-based stress reduction (MBSR) is a meditative practice which has been shown across multiple medical domains to effectively reduce the symptoms of anxiety, depression, and PTSD [8]. In present times, MBSR can be delivered via web-based application on any smart device.

We hypothesize that symptoms of anxiety, depression, and PTSD are common among patients during and after NP disease course and can be quantified reliably with established screening instruments. Furthermore, we hypothesize that an MBSR-based intervention can decrease the incidence and severity of the symptoms of anxiety, depression, and PTSD in a necrotizing pancreatitis population. There is a paucity of literature examining mental health in this patient population.

QUALITY OF LIFE AFTER NECROTIZING PANCREATITIS

The limited existing literature suggests, not surprisingly, that quality of life (QoL) is impaired following NP. Existing factors contributing to decreased QoL include persistent abdominal pain, bowel problems, poor appetite, weight loss, and increased rates of disability. Szentkerszty et al identified additional risk factors associated with decreased QoL after NP episode including older age, significant weight loss after illness onset, poor appetite, and female sex [9]. Decreases in QoL persist long after AP diagnosis: at 1 year after AP diagnosis, Guogol et al identified a 24% rate of abdominal pain, with 41% of patients reporting pain-

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related interference with work or daily activities [10]. A second study from the same group found that patients with AP had significantly lower physical health related QoL at 14 months after hospital discharge [11]. Although these studies establish a clinical foundation for impaired mental health, no studies specifically examine mental health diagnoses following NP diagnosis. The intuitive connection between poor QoL and psychiatric comorbidity was borne out in studies by Wang et al, who examined post-ICU psychiatric comorbidity in a non-NP patient population and found a correlation between poor QoL and psychiatric comorbidity [12].

POST-ICU SYNDROME

Within our NP population, we have identified a very high rate of organ failure and need for ICU treatment [2]. Although no NP-specific literature exists, a parallel body of literature describes post-ICU syndrome. This entity is defined as "new or worsening problems in physical, cognitive, or mental health status arising after a critical illness and persisting beyond acute care hospitalization" [13]. Significant overlap exists between NP disease course and disease requiring ICU care. These similarities include severe illness requiring ventilatory and hemodynamic support, organ failure, and prolonged hospitalization. The overlap between NP disease course and illness requiring critical care makes it reasonable to postulate that characteristics of post-ICU syndrome pervade in the NP population as well (Fig 1).

A review by Desai et al examined existing literature on mental health outcomes in ICU survivors, finding a 24% rate of anxiety, 28% rate of clinically significant depressive symptoms, and 22% rate of PTSD. Depression and anxiety tended to improve within the first year following illness, whereas PTSD symptoms persisted beyond 1 year [4]. Risk factors identified for poor mental health outcomes in this study included pre-ICU psychiatric symptoms, younger age, and female sex. A mechanistic underpinning explaining the development of mental health disorders in this population is extremely difficult to establish, but the authors posit cerebral hypoxia, inflammation, hypoglycemia, and benzodiazepine use as potential contributors.

A longitudinal cohort study examined depression and PTSD using the Beck Depression Inventory II and Post-Traumatic Stress Disorder Checklist-Event Specific Version within the BRAIN-ICU study population. This study found similarly high rates of depression as Desai, with 37% of patients having at least mild depression at 3 months and 33% at 1 year after discharge from hospitalization requiring ICU treatment [14]. Wunsch et al examined mental health outcomes in a large cohort of 9,912 critical illness survivors. Their findings are in line with those

of Desai and the BRAIN-ICU study with a reported hazard ratio of 21.8 for new psychiatric diagnoses following ICU study compared with the general population [15]. Collectively, the existing data suggest that ICU treatment is a significant risk factor for mental health sequelae, including depression, anxiety, and PTSD. The frequent necessity for ICU treatment in NP patients is likely to contribute to mental health sequelae observed in this patient population.

SCREENING INSTRUMENTS

Several validated screening instruments for anxiety, depression, and PTSD are in common use (Table 1); these instruments are logical choices to assess for symptoms of these disorders in the NP population. GAD-7 is a 7-question screening instrument for anxiety with a reported sensitivity of 89% and specificity of 82% [6]. PHQ-9 is a 9-question screen for major depressive disorder with a reported sensitivity of 88% and specificity of 85% [5]. PCL-5 is the latest iteration of the well-established PCL that has been recently updated for consistency with DSM-5 diagnostic criteria and has high validity and reliability [7].

The GAD-7, PHQ-9, and PCL-5 are used commonly in the psychiatry outpatient setting to screen for anxiety and depression. These screening tools have not been specifically validated in a necrotizing pancreatitis population; however, they are highly sensitive screening instruments with many advantages in the context of NP. As each screening tool takes about 1 minute for a patient to complete, these tools can be rapidly and easily provided to NP patients in both the inpatient and outpatient setting. In the typically prolonged NP disease course, these easily administered instruments are ideal to longitudinally evaluate the progression of mental health symptoms via frequent rescreening. We recommend screening patients during their index hospitalization shortly after disease onset as well as rescreening every 6 to 8 weeks during NP disease course to fully characterize the course of mental health symptoms throughout NP (Fig 2). Future studies may seek to validate these screening instruments in the NP patient population.

MINDFULNESS-BASED STRESS REDUCTION

Defining the incidence of symptoms of anxiety, depression, and PTSD in the NP population is critically necessary; however, perhaps more important is identifying feasible interventions to improve mental health outcomes. In this context, MBSR represents an exciting potential therapy. MBSR has been defined as a meditative practice focused on cultivating acceptance of thoughts, feelings, and sensations through moment-to-moment bodily awareness. MBSR has demonstrated efficacy in improving mental health in oncology, geriatric, veteran, chronic pain, and health care provider populations. MBSR has been shown to reduce rates of anxiety, depression, and PTSD [8] as well as improve resiliency and reduce opioid utilization. The mechanistic underpinning of MBSR's efficacy is emerging; growing data suggest that MBSR produces a measurable decrease in inflammatory markers. This finding is especially interesting in the NP population, as many of the sequelae of NP leading to critical illness are secondary to the massive inflammatory insult produced by pancreatic necrosis.

MBSR is a logical intervention to attenuate NP-associated psychiatric comorbidity. Mindfulness applications are widely available at little to no cost across multiple web-based and smart device platforms. The low barrier to entry of these applications is complemented by customizability: mindfulness meditations have varied foci, including breathing techniques,

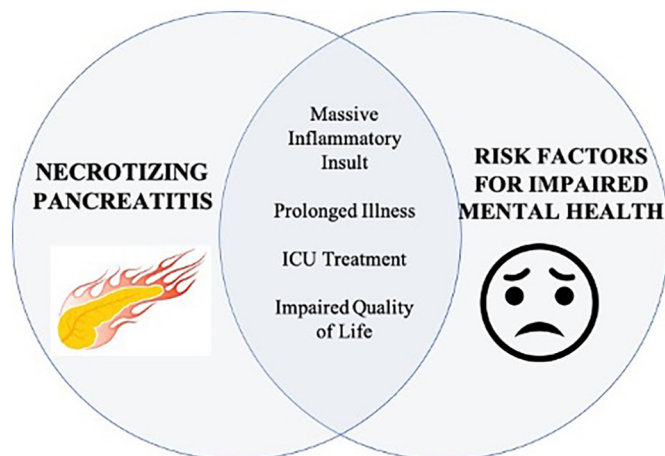


Fig 1. Overlap between necrotizing pancreatitis disease course and risk factors for impaired mental health following severe illness.

Table 1
Mental health diagnoses and respective associated screening tools

Pancreatitis-associated disorder	Screening tool
Anxiety	General Anxiety Disorder-7 (GAD-7)
Depression	Patient Health Questionnaire-9 (PHQ-9)
Stress	PTSD Checklist for DSM-5 (PCL-5)

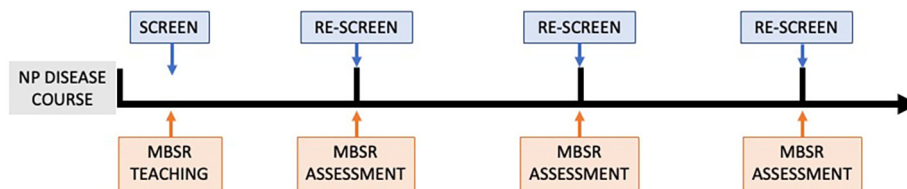


Fig 2. Suggested schematic for screening for pancreatitis-associated anxiety, depression, and stress (PADS) and assessing the feasibility of MBSR as a PADS-focused intervention.

sleep techniques, resiliency, and bodily awareness. Finally, MBSR aligns with larger trends in health care toward wider implementation of virtual platforms to deliver care, especially in the Covid and post-Covid era.

Mindfulness interventions have the potential to be widely used in the NP patient population and to significantly improve NP patients' mental health. Initial attempts to assess MBSR as a therapy for PADS should begin with an assessment of the feasibility of MBSR as an intervention. This would entail an initial teaching session early in disease course in which MBSR is introduced and explained and patients are encouraged to download and use an MBSR-based app throughout their NP disease course. As PADS screens are repeated, the frequency of use of the MBSR-based apps will be assessed as well (Fig 2).

This schemata for introducing and evaluating MBSR emphasizes a low barrier to entry for both the patient as well as the physician introducing the concept of MBSR to patients. If initial studies demonstrate a lack of feasibility with this approach, more robust MBSR teaching or alternative interventions may be considered. Physicians providing care for NP patients may begin to incorporate this approach to assessing and treating impaired mental health in their patient population. In addition to this approach, severe deterioration of mental health should continue to prompt formal psychiatric evaluation and intervention.

In conclusion, necrotizing pancreatitis is a severe disease which impairs QoL. High rates of severe illness requiring critical care treatment place NP patients at especially high risk for an increase in symptoms of anxiety depression and PTSD, as well as mental health challenges that remain to be fully elucidated in this patient population. Mindfulness-based stress reduction is an especially well-suited intervention to decrease the symptoms of these conditions in NP patients. Physicians should be cognizant of potential psychiatric sequelae in NP patients and direct therapy accordingly. Establishing the incidence of mental health disorders and implementing strategies to improve mental health outcomes are critical to holistic care of necrotizing pancreatitis patients.

Author Contribution

SPM contributed to project conceptualization, data curation, formal analysis, methodology, and drafted and revised the manuscript. AMM contributed to project conceptualization, methodology, and revision of the manuscript. KAM contributed to project conceptualization, data curation, and revision of the manuscript. NJZ contributed to project conceptualization, formal analysis, methodology, supervision of the project, and drafted and revised the manuscript.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Ethics Approval

This study was reviewed by the Indiana University Institutional Review Board and granted exempt status.

References

- [1] Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo Jr CA. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas*. 2007;35(4):302–7.
- [2] Maatman RA TK, Ceppa EP, Easler JJ, Gromski MA, House MG, Nakeeb A, et al. The continuum of complications in survivors of necrotizing pancreatitis. *Surgery*. 2020; 168(6):1032–40.
- [3] Chung CR, Yoo HJ, Park J, Ryu S. Cognitive impairment and psychological distress at discharge from intensive care unit. *Psychiatry Investig*. 2017;14(3):376–9.
- [4] Desai LT SV, Needham DM. Long-term complications of critical care. *Crit Care Med*. 2011;39(2):371–9.
- [5] Kroenke SR K, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606–13.
- [6] Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166(10):1092–7.
- [7] Blevins CA, et al. The Posttraumatic Stress Disorder Checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress*. 2015;28(6):489–98.
- [8] Boyd JE, Lanius RA, McKinnon MC. Mindfulness-based treatments for posttraumatic stress disorder: a review of the treatment literature and neurobiological evidence. *J Psychiatry Neurosci*. 2018;43(1):7–25.
- [9] Szentkereszty Z, Agnes C, Kotán R, Gulácsi S, Kerekes L, Nagy Z, et al. Quality of life following acute necrotizing pancreatitis. *Hepatogastroenterology*. 2004;51(58): 1172–4.
- [10] Gougol A, Machicado JD, Matta B, Paragomi P, Pothoulakis I, Slivka A, et al. Prevalence and associated factors of abdominal pain and disability at 1-year follow-up after an attack of acute pancreatitis. *Pancreas*. 2019;48(10):1348–53.
- [11] Machicado JD, Gougol A, Stello K, Tang G, Park Y, Slivka A, et al. Acute pancreatitis has a long-term deleterious effect on physical health related quality of life. *Clin Gastroenterol Hepatol*. 2017;15(9):1435–1443.e2.
- [12] Wang S, Mosher C, Perkins AJ, Gao S, Lasiter S, Khan S, et al. Post-intensive care unit psychiatric comorbidity and quality of life. *J Hosp Med*. 2017;12(10):831–5.
- [13] Needham DM, Davidson J, Cohen H, Hopkins RO, Weinert C, Wunsch H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med*. 2012;40(2):502–9.
- [14] Jackson JC, Pandharipande PP, Girard TD, Brummel NE, Thompson JL, Hughes CG, et al. Depression, post-traumatic stress disorder, and functional disability in survivors of critical illness in the BRAIN-ICU study: a longitudinal cohort study. *Lancet Respir Med*. 2014;2(5):369–79.
- [15] Wunsch H, Christiansen CF, Johansen MB, Olsen M, Ali N, Angus DC, Sørensen HT. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA*. 2014;311(11):1133–42.