Pneumatosis Intestinalis Predictive Evaluation Study: A multicenter epidemiologic study of the American Association for the Surgery of Trauma

Paula Ferrada, MD, Rachael Callcut, MD, Graciela Bauza, MD, Karen R. O'Bosky, MD, Xian Luo-Owen, PhD, Nicky J. Mansfield, MD, Kenji Inaba, MD, Jason Pasley, DO, Nikolay Bugaev, MD, Bruno Pereira, MD, Forrest O. Moore, MD, Jinfeng Han, RN, Amelia Pasley, DO, Joseph DuBose, MD, *and* **AAST Multi-institutional Trials Committee***, Richmond, Virginia*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint providership of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Of the *AMA PRA Category 1 Credit*™ listed above, a maximum of 1 credit meets the requirements for self-assessment.

Credits can only be claimed online

AMERICAN COLLEGE OF SURGEONS

Inspiring Quality: Highest Standards, Better Outcomes

100+*years*

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery*, participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "e-Learning/MOC" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma Acute Care Surg* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a `commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12'months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you'perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff

Ernest E. Moore, Editor: PI, research support and shared U.S. patents Haemonetics; PI, research support, TEM Systems, Inc. Ronald V. Maier, Associate editor: consultant, consulting fee, LFB Biotechnologies. Associate editors: David Hoyt and Steven Shackford have nothing to disclose. Editorial staff: Jennifer Crebs, Jo Fields, and Angela Sauaia have nothing to disclose."

Author Disclosures

The authors have nothing to disclose.

Reviewer Disclosures

The reviewers have nothing to disclose.

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $25.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

BACKGROUND: Our group has previously published a retrospective review defining variables predictive of transmural bowel ischemia in the setting of pneumatosis intestinalis (PI). We hypothesize this prospective study will confirm the findings of the retrospective review, enhancing legitimacy to the predictive factors for pathologic PI previously highlighted.

METHODS: Data were collected using the Research Electronic Data Capture. Forward logistic regression was utilized to identify independent predictors for pathologic PI. Statistical significance was defined as $p \leq 0.05$.

RESULTS: During the 3-year study period, 127 patients with PI were identified. Of these, 79 had benign disease, and 49 pathologic PI defined by the presence of transmural ischemia during surgical exploration or autopsy. Laboratory values such as elevated international normalized ratio (INR), decreased hemoglobin, and a lactate value of greater than 2.0 mmol/L were predictive of pathologic PI, as well as clinical factors including adynamic ileus, peritoneal signs on physical examination, sepsis, and hypotension. The location was also a significant factor, as patients with small bowel PI had a higher incidence of transmural ischemia than colonic PI. On multiple logistic regression, lactate value of greater than 2.0 mmol/L (odds ratio, 5.1, 1.3–19.5; $p = 0.018$), elevated INR (odds ratio, 3.2, 1.1–9.6; $p = 0.031$), peritonitis (15.0, 2.9–78; $p = 0.001$), and decreased hemoglobin (0.70, 0.50–0.97, 0.031) remained significant predictors of transmural ischemia (area under the curve, 0.90; 0.83–0.97). A lactate value of 2.0 mmol/L or greater and peritonitis are common factors between the retrospective review and this prospective study.

CONCLUSIONS: We recommend surgical exploration to be strongly considered for those PI patients presenting also with a lactate greater than 2 mmol/L and/or peritonitis. We suggest strong suspicion for necrosis in those patient with PI and small bowel involvement, ascites on computed tomography scan, adynamic ileus, anemia, and a high INR. (*J Trauma Acute Care Surg.* 2017;82: 451–460. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic study, level II; therapeutic study, level II.

KEY WORDS: Pathologic pneumatosis intestinalis; pneumatosis intestinalis and mortality; pneumatosis intestinalis and necrosis; pneumatosis intestinalis and surgery.

The pathogenesis of pneumatosis intestinalis (PI) or air in the intestinal wall is poorly understood as it is the significance of this finding when guiding surgical therapy.[1] In the last decade, PI is believed to be more common than previously reported, since the advancements in imaging with thin-cut computed tomography (CT).[2–4] Furthermore, to date, there are no protocols to guide surgical intervention.[2–4]

The true incidence of PI is unknown.[5–12] Moreover, the clinical significance of PI can vary from necrotic bowel to a benign finding.[13–15] Distinguishing pathologic from benign PI has largely been reliant on clinical acumen with little scientific data to guide management.[13–15]

The present group has devoted the last few years to understand the significance of this finding in changing surgical management, in conjunction with other clinical predictors of pathology.[1]

We previously published a retrospective review of 500 patients with PI. In this review, we identified a lactate greater than 2.0 mmol/L as the strongest independent predictors of pathologic PI.[1] Other factors such as peritonitis, hypotension or vasopressor need, acute renal failure, active mechanical ventilation, and absent bowel sounds also demonstrated significance. To validate these findings, a prospective, multicenter study was undertaken. We hypothesize this prospective study will confirm the findings of the retrospective review, enhancing legitimacy to the predictive factors for pathologic PI previously highlighted.

PATIENTS AND METHODS

This was a prospective multicenter study conducted under the sponsorship of the Association for the Surgery of Trauma. The study protocol was approved by the Association for the Surgery of Trauma Multi-institution Trials Committee. Seven centers enrolled patients, and each participating center obtained approval from its institutional review board. We used the Research Electronic Data Capture to store and analyze the data of these patients.

The primary aim of the study was to prospectively evaluate patients with PI identified on CT scan to determine patient, clinical presentation, and radiographic imaging factors associated with pathologic PI. Pathologic PI was defined a priori as either transmural ischemia confirmed at the time of operative intervention or if it was identified as the cause of death in those not undergoing operation during autopsy. Secondary study aims included comparison of mortality, length of stay (LOS), and ventilator days in those with and without pathologic PI.

Inclusion criteria were any adult patient (≥18 years old) identified by a staff radiologist to have PI or gas in the bowel wall on imaging The patients who did not have available CT data were not included in the analysis involving location of PI or additional CT radiographic abnormalities.

Exclusion criteria included pregnant women, prisoners, and children. Demographic data and medical history including an extensive list of preexisting conditions, clinical presentation

Submitted: July 21, 2016, Revised: December 5, 2016, Accepted: December 8, 2016, Published online: January 3, 2017.

From the Virginia Commonwealth University, Richmond, Virginia (P.F., J.H.); University of California, San Francisco (R.C.); University of Pittsburg Medical Center, Pittsburg, Pennsylvania (G.B.); Loma Linda University and Medical Center, Loma Linda, California (K.R.O., X.L-O.); Keck School of Medicine at the University of Southern California, Los Angeles, California (N.J.M., K.I.); University of Maryland Medical Center, Baltimore, Maryland (J.P., A.P.); Tuffs University, Medford, Massachusetts (N.B.); University of Campinas, Campinas, São Paulo, Brazil (B.P.); Chandler Regional Medical Center, Chandler, Arizona (F.O.M.); and University of California, Davis, California (J.D.).

This study was presented at the75th annual meeting of the American Association for the Surgery of Trauma, September 14–17, 2016, in Waikoloa, Hawaii.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Paula Ferrada, MD, FACS, Virginia Commonwealth University, 417 N 11th St, Richmond, VA 23298; email: pferrada@mcvh-vcu.edu.

DOI: 10.1097/TA.0000000000001360

including detailed radiographic findings, interventions, and outcomes were collected. Attending radiology interpretation findings were utilized for radiographic description of PI location and CT findings. An a priori standard set of definitions was utilized across centers for definitions of comorbidities, clinical presentation, and outcomes. From these, additional categorical variables were created grouping relevant primary data (Table 1; and Supplemental Digital Content 1, http://links.lww.com/TA/A892). Those with and without pathologic PI were compared using Mann-Whitney U-test for testing distribution of continuous variables, median test (independent-sample test of medians), and Fisher exact test for categorical variables. Multilevel logistic regression models nested for center effect were utilized to identify independent predictors for pathologic PI. Variables with significance at the $p < 0.1$ level on univariate analysis and clinically relevant variables from prior studies were considered for selection in the multiple logistic regression. Area under the receiver operating curves were used to compare predictive models. Goodness of fit was measured with Hosmer and Lemeshow test, and only appropriately fit models are included. Statistical significance was defined as $p \leq 0.05$.

TABLE 1. Grouping of Patient Comorbidity, Clinical Presentation, and Radiographic Findings

Category	Included Variables
Comorbidity	
Pulmonary	Asthma or bronchitis or emphysema or pulmonary fibrosis or cystic fibrosis
Renal	Chronic renal failure
GI	Inflammatory bowel disease or ulcerative colitis or peptic ulcer or Crohn disease
Immunosuppression	Scleroderma or systemic lupus erythematosus or AIDS or leukemia or any transplant (bone marrow, kidney, liver, cardiac, lung) or current immunosuppression medication
Current immunosuppressive medication	Current steroid use or current chemotherapy
Malignancy	Any malignancy history
Any active systemic disease pre-existing	Scleroderma or systemic lupus erythematosus or AIDS or leukemia or chronic renal failure
Any comorbidity	Pulmonary or renal or GI or immunosuppression or any active systemic disease preexisting or malignancy
Physical examination	
Peritoneal physical examination	Abdominal rigidity or peritonitis
Abnormal physical examination	Abdominal rigidity or peritonitis or distention or heme-positive stools
Clinical presentation	
Hemodynamic instability	Hypotension or current pressor use
Hypotension	Systolic blood pressure <90 mm Hg
Any active infection	Pneumonia or *Clostridium difficile* colitis or other colitis or catheter or blood stream or urinary tract infections
End organ dysfunction	Multiple organ failure, or acute renal failure, or acute hepatic failure or acute respiratory distress syndrome
Radiographic findings	
Small bowel PI	Location including duodenum or jejunum or ileum
Colon PI (excluding rectum)	Location including cecum or appendix or ascending or transverse or descending or sigmoid
Right colon PI	Location including cecum or ascending or appendix
Left colon PI	Location including descending or sigmoid
CT abnormality excluding PI	Bowel wall thickening or dilated bowel or ascites or arterial or venous mesenteric occlusion or hepatic portal gas or retroperitoneal air or portomesenteric venous gas or free peritoneal air
CT bowel abnormality only	Bowel wall thickening or dilated bowel

RESULTS

During the 3-year study period, 127 patients with PI were identified. Computed tomography scan was the mode of imaging in 117 (92%) of 127 patients. Benign PI was found in 79 patients (62.2%), and 48 patients (37.8%) had pathologic PI defined by the presence of transmural ischemia during surgical exploration or autopsy. There was no statistical difference between age and comorbidities between groups with the exception of a higher incidence of chronic renal failure in those with pathologic PI (Table 2).

For the 10 patients who did not get CT scans, 8 patients had plain radiographs demonstrating concern for PI, and in 2 patients, the imaging modality was not reported.

Operative Intervention and Mortality Outcomes

Overall mortality was 34% in the pathologic PI group compared with 13.9% in the benign PI group ($p = 0.013$). Among the 79 patients classified as having benign PI, operative intervention was not offered in 49 patients (62%), and in the remaining 30 patients, 27 patients underwent operative intervention. None of the 11 patients in the benign PI group who died were found to have transmural ischemia as a contributing cause of death. In contrast, all those who died in the pathologic PI group did. Five patients in the pathologic PI group were not offered operative intervention as a result of futility and died with transmural bowel ischemia. Of the 43 patients with pathologic PI undergoing operative intervention, 91% (39 patients) had a bowel resection performed, and 4 patients did not as their disease was judged to be nonsurvivable intraoperatively. As expected patients with pathologic PI had an increased hospital LOS and intensive care unit LOS than those patients with benign disease.

Clinical, Laboratory, and Radiographic Factors Predictive of Pathologic PI

Clinical factors including hemodynamic instability (pressors or hypotension), hypotension alone, sepsis, peritoneal abdominal examination (abdominal rigidity or peritonitis), peritonitis alone, abdominal rigidity alone, and the presence of an adynamic ileus were different between those with and without pathologic PI (Table 3). Laboratory values including higher white blood cell (WBC) count, lower hemoglobin, increased potassium, decreased bicarbonate, elevated creatinine, elevated blood urea nitrogen, lactate 2 mmol/L or greater, and a higher international normalized ratio (INR) were also predictive of pathologic PI (Table 4). The radiographic location was also a significant factor, as

TABLE 2. Demographic, Comorbidity, and Outcomes for Those With and Without Pathologic PI

	n	Benign PI (n = 79)	Pathologic PI (n = 48)	*p*
Age, median (range), y	127	55.0 (18–86)	60.5 (22–87)	0.113*
Pulmonary disease	127	19 (24.1%)	7 (14.6%)	0.259
Asthma	127	5 (6.3%)	4 (8.3%)	0.462
Bronchitis	127	1 (1.2%)	0	1.000
Emphysema	127	6 (7.5%)	3 (6.3%)	1.000
Pulmonary fibrosis	127	8 (10.1%)	1 (2.1%)	0.152
Cystic fibrosis	127	0	0	
Renal				
Chronic renal failure	127	5 (6.3%)	10 (20.8%)	0.022
GI	127	3 (3.8%)	4 (8.3%)	0.425
Inflammatory bowel disease	127	1 (1.3%)	0	1.000
Ulcerative colitis	127	1 (1.3%)	2 (4.2%)	0.556
Peptic ulcer	127	1 (1.3%)	1 (2.1%)	1.000
Crohn disease	127	1 (1.3%)	1 (2.1%)	1.000
Diverticulitis	127	0	1 (2.1%)	0.378
Any transplant	127	12 (15.2%)	4 (8.3%)	0.409
Transplant—bone marrow	127	0	0	
Transplant—kidney	127	0	0	
Transplant—liver	127	3 (3.8%)	3 (6.35)	0.672
Transplant—cardiac	127	0	0	
Transplant—lung	127	9 (11.4%)	1 (2.1%)	0.088
Graft-versus-host disease	127	1 (1.3%)	0	1.000
Immunosuppression medications	127	18 (22.8%)	12 (25.0%)	0.831
Current steroid use	127	18 (22.8%)	10 (20.8%)	0.829
Current chemotherapy	127	6 (7.6%)	4 (8.3%)	1.000
History of steroids	127	20 (25.3%)	10 (20.8%)	0.668
History of chemotherapy	127	9 (11.4%)	4 (8.3%)	0.765
Malignancy	79**	19 (42.2%)	15 (44.1%)	1.000
Any systemic disease preexisting (including chronic renal failure)	127	11 (13.9%)	13 (27.0%)	0.100
Scleroderma	127	3 (3.8%)	0	0.289
Systemic lupus erythematosus	127	0	1 (2.1%)	0.378
AIDS	127	4 (5.1%)	0	0.296
Leukemia	127	0	2 (4.2%)	0.141
Any comorbidity	79**	31 (68.9%)	24 (70.6%)	1.000
LOS				
Hospital LOS	124	8 (0–113)	11 (0–95)	0.0001
ICU LOS	124	0 (0–113)	11 (0–95)	0.0001
Ventilator days	124	0 (0–113)	4 (0–66)	<0.0001
Mortality	126	11 (13.9%)	16 (34.0%)	0.013

*Mann-Whitney test for continuous variable; all others Fisher exact test for categorical variables.
**n = 45 with benign PI; n = 34 with pathologic PI.
ICU, intensive care unit.

patients with small bowel PI had a higher incidence of transmural ischemia than PI at all colonic locations (Table 4). Hepatic portal venous gas was the only other CT scan finding different between those with pathologic PI and those without (Table 4).

On multilevel logistic regression, a lactate value of 2.0 mmol/L or greater (odds ratio [OR], 5.0, 1.1–22.4; p = 0.037), elevated INR (OR, 4.1; 1.2–13.9; p = 0.023), peritonitis (OR, 35.8; 3.0–407; p = 0.005), and decreased hemoglobin (OR, 0.7; 0.5–0.9, 0.023) remained significant predictors of transmural ischemia in the final predictive model (area under the curve [AUC], 0.92; 0.87–0.98) (Table 5). When excluded peritonitis as a predictor variable in the models, a lactate value of 2.0 mmol/L or greater (OR, 5.0; 1.5–17; p = 0.009), elevated INR (OR, 2.9; 1.1–7.3; p = 0.030), and hemoglobin (OR, 0.7; 0.5–0.9, 0.018) continue to represent significant predictors of transmural ischemia (AUC 0.85; 0.76–0.94) (Table 5). The vast majority of the patients in the study did not present with peritonitis on initial physical examination (80% no peritonitis, 102/127 patients). When considering only these patients without peritonitis, a lactate value of 2.0 mmol/L or greater, elevated INR, and decreased hemoglobin all trended toward being the most significant predictors (AUC, 0.87; 0.79–0.95). Table 6 shows the comparison of the independent predictors of pathologic PI between models

TABLE 3. Clinical Presentation and Physical Examination Findings for Those With and Without Pathologic PI

	n	Benign PI (n = 79)	Pathologic PI (n = 48)	*p*
Clinical presentation				
Hemodynamic instability	127	12 (15.2%)	19 (39.6%)	**0.003**
Hypotension	127	10 (12.7%)	17 (35.4%)	**0.003**
Active medications—on pressors	127	10 (12.7%)	10 (20.8%)	0.315
Mechanical ventilation	127	8 (10.1%)	11 (22.9%)	0.071
Active medications—on antibiotics	127	27 (34.2%)	18 (37.5%)	0.707
Any infection	127	17 (21.5%)	9 (18.8%)	0.822
Pneumonia	127	6 (7.6%)	2 (4.2%)	0.709
Bloodstream	127	8 (10.1%)	7 (14.6%)	0.572
Catheter/urinary tract infection	127	2 (2.5%)	2 (4.2%)	0.633
C. difficile colitis	127	0	0	
Other colitis	127	5 (6.3%)	1 (2.1%)	0.408
Hepatic failure	127	6 (7.6%)	5 (10.4%)	0.746
Acute lung injury or acute respiratory distress syndrome	127	3 (3.8%)	6 (12.5%)	0.081
Acute renal failure	127	14 (17.7%)	11 (22.9%)	0.497
Sepsis	127	13 (16.5%)	16 (33.3%)	**0.032**
Multiorgan failure	127	8 (10.1%)	9 (18.75%)	0.187
Any end-organ dysfunction	127	15 (19.0%)	16 (33.3%)	0.089
Physical examination findings				
Abnormal physical examination	127	47 (59.5%)	37 (77.1%)	0.052
Peritoneal physical examination	127	8 (10.1%)	24 (50.0%)	**<0.001**
Distention	127	44 (55.7%)	31 (64.6%)	0.357
Peritonitis	127	5 (6.3%)	19 (39.6%)	**<0.001**
Diarrhea	127	11 (13.9%)	8 (16.7%)	0.798
Absent bowel sounds	127	5 (6.3%)	8 (16.7%)	0.075
Abdominal rigidity	127	5 (6.3%)	14 (29.2%)	**0.001**
Constipation	127	18 (22.8%)	4 (8.3%)	0.052
High-pitched bowel	127	1 (1.3%)	1 (2.1%)	1
Heme-positive stool	127	5 (6.3%)	3 (6.3%)	1
Adynamic ileus	127	0	6 (12.5%)	**0.002**
Pseudo-obstruction	127	1 (1.3%)	4 (8.3%)	0.067

Boldface indicates statistically significant.

including and not including patients presenting with peritonitis controlled for center effect.

DISCUSSION

Guiding the clinician to take a lifesaving decision regarding timing of surgical intervention in pathologic PI is pivotal. Although there is still lack of clarity of the cause of PI, this prospective work in conjunction without previous publication shed some light in issues that can support a course of therapy.[16] In patients who have benign PI without any clinical significant findings, the clinical decision making is easier than when you have patients with PI who might have ischemia but not yet transmural necrosis.[4,16,17] Interestingly, patients who had small bowel PI had an increased chance of having bowel necrosis than those with colonic PI. This might be a consequence in the underlying factor that led to bowel ischemia. The bowel undergoes necrosis by layers, starting from the mucosa and progressing forward until full wall necrosis results. If there is some ischemia of the colon secondary to overall hypoperfusion, but this factor is corrected, this can reverse the lack of perfusion not resulting in transmural necrosis.[18] In the other hand, if the inciting factor is a mechanical obstruction, then surgical intervention is essential in avoiding inevitable progression of the ischemia to necrosis and perforation that would result in further morbidity and mortality.[19]

Adynamic ileus when suspecting ischemia is an ominous sign, because lack of motility indicates progression to necrosis. However, it was not significant in multiple logistic regression in this study. This may reflect an element of documentation bias as there is no definitive test for ileus. In contrast, peritonitis was the strongest predictor of ischemia and would perhaps suggest that in some cases conservative treatment has been tried for too long.[18] Although hypotension or hemodynamic instability is associated with shock,[20] it was not an independent predictor of ischemia in any of the models considered (Table 5). Based on both our previous retrospective study and the present prospective validation, laboratory abnormalities need to be strongly considered when deciding for surgery.[1] Lactate as a measurement of perfusion has been identified in both studies as a factor predicting necrosis. Other studies have similar findings with elevated lactate and PI associated with mortality exceeding 80%.[21] One unanticipated finding in the present study was the predictive role of decreased hemoglobin. It was a predictor of pathologic PI throughout all the best predictive models. Physiologically, this

TABLE 4. Laboratory and Radiographic Findings of Those With and Without Pathologic PI

	n	Benign PI (n = 79)	Pathologic PI (n = 48)	*p*
Laboratory findings				
WBC count, mcL	127	10.0 (3–29)	12.7 (0–3,600)	0.027
Hemoglobin, g/dL	127	11.9 (4–17)	10.3 (7–17)	0.018
Hematocrit, g/dL	127	36.0 (21–50)	31.1 (19–62)	0.02
Platelets 103/microliter	127	223 (10–1,072)	237 (10–822)	0.557
Sodium, mEq/L	127	137 (34–155)	137 (123–149)	0.655
Potassium, mEq/L	127	4.0 (2.6–5.6)	4.3 (2.9–7.0)	0.028
Chloride, mEq/L	126	101 (60–122)	99 (91–112)	0.106
Bicarbonate, mEq/L	127	25 (5–138)	22 (9–44)	0.03
Blood urea nitrogen, mg/dL	125	20 (4–100)	38 (5–360)	0.0001
Creatinine, mg/dL	126	0.97 (0.31–6.2)	1.67 (.38–6.88)	0.0001
pH	56	7.38 (7–8)	7.35 (7–8)	0.510
PaO_2	55	100 (38–316)	93.0 (31–500)	0.657
PaCO2	55	36 (18–56)	36 (21–88)	0.918
Base deficit	52	0.85 (−0.23 to 12)	1.9 (−14 to 22)	0.201
Lactate	109	1.5 (1–28)	2.5 (1–14)	0.0001
Lactate ≥2 mmol/L	109	23 (35.4%)	30 (68.2%)	0.001
Partial thromboplastin time	57	29.0 (11–69)	31.45 (1–76)	0.361
INR	85	1.11 (.9–4.0)	1.4 (1–13.5)	0.006
Aspartate aminotransferase, units per liter	101	31.5 (7–265)	30.0 (12–1,140)	0.428
Alanine aminotransferase, units per liter	99	26.5 (4–251)	22.0 (6–680)	0.534
Bilirubin (direct), mg/dL	57	0.3 (0–3)	0.4 (0.1–8.5)	0.372
Bilirubin (indirect), mg/dL	55	0.4 (0–1.0)	0.5 (0.1–8.2)	0.112
Time between laboratory findings + findings (h)	123	4 (0–96)	2 (0–30)	0.006
Radiographic findings				
Location—gastric	127	2 (2.5%)	2 (4.2%)	0.633
Location—any small bowel	127	32 (40.5%)	29 (60.4%)	**0.043**
Duodenum	127	3 (3.8%)	4 (8.3%)	0.425
Jejunum	127	27 (34.2%)	19 (39.6%)	0.572
Ileum	127	21 (26.6%)	21 (43.8%)	0.054
Any colon (excludes rectum)	127	47 (59.5%)	28 (58.3%)	1
Right colon	127	39 (49.4%)	21 (43.8%)	0.585
Left colon	127	10 (12.7%)	7 (14.6%)	0.792
Cecum	127	26 (32.9%)	14 (29.2%)	0.698
Ascending colon	127	31 (39.2%)	20 (41.7%)	0.853
Transverse colon	127	13 (16.5%)	4 (8.3%)	0.283
Descending colon	127	8 (10.1%)	4 (8.3%)	1
Sigmoid colon	127	4 (5.1%)	7 (14.6%)	0.101
Rectum	127	3 (3.8%)	0	0.289
Appendix	127	1 (1.3%)	0	1
Diffuse PI	127	31 (39.2%)	17 (35.4%)	0.572
Bowel wall thickening	127	22 (27.8%)	17 (35.4%)	0.429
Dilated bowel	127	36 (45.6%)	23 (47.9%)	0.855
Ascites	127	8 (10.1%)	9 (18.8%)	0.187
Arterial or venous mesenteric occlusion	127	2 (2.5%)	3 (6.3%)	0.365
Hepatic portal gas	127	6 (7.6%)	16 (33.3%)	**<0.001**
Retroperitoneal air	127	3 (3.8%)	1 (2.1%)	1
Portomesenteric venous gas	127	16 (20.3%)	14 (29.2%)	0.285
Free peritoneal air	127	14 (17.7%)	10 (20.8%)	0.816
Any other abnormality except PI	127	58 (73.4%)	44 (91.7%)	**0.012**
CT other abnormality bowel	127	49 (62.0%)	32 (66.7%)	0.704

TABLE 5. Candidate Models for Prediction of Pathologic PI Controlling for Center Effect

Model	n	AUROC (95% CI)	Model Components
Retrospective study model	109	0.713 (0.615–0.810)	Lactate ≥2 mmol/L,* AKI, hemodynamic instability, mechanical ventilation, absent bowel sounds
Laboratory only	79	0.831 (0.739–0.923)	Hemoglobin,* INR,* WBC, potassium, creatinine, lactate (continuous)
Laboratory only including lactate ≥2 mmol/L	79	0.830 (0.739–0.921)	Hemoglobin,* lactate ≥2 mmol/L,* INR,** WBC, potassium, creatinine
Examination and laboratory only	80	0.913 (0.850–0.975)	Peritonitis,† hemoglobin,* lactate ≥2 mmol/L,* INR*
Final model	80	0.852 (0.764–0.939)	Hemoglobin,* lactate ≥2 mmol/L,* INR,* small bowel PI, AKI, ascites
Final model + peritonitis as predictor	80	0.924 (0.866–0.982)	Peritonitis,* hemoglobin,* lactate ≥2 mmol/L,* INR,* Small bowel PI, AKI, ascites

Shaded rows indicate peritonitis was included as a predictor variable in the model.
*Independent predictors in model at $p < 0.05$, controlled for center effect.
**Independent predictor in model at $p < 0.2$, controlled for center effect.
†Independent predictors in model at $p < 0.1$, controlled for center effect.
AKI, acute kidney injury; CI, confidence interval.

likely reflects sloughing of the mucosa and resultant bleeding into the gastrointestinal (GI) tract at the end points of ischemia. Other laboratory measurements including an elevated INR have been shown to be a product of decreased perfusion and shock.[20] All these predictors of pathologic PI are clinical factors that of importance in any patient with abdominal complaints. Conversely, radiological patterns of PI differ in how to predict bowel necrosis[13,22] and did not appear to be as useful in distinguishing pathologic PI from benign PI in the context of the other independent predictors.

The conditional probabilities of pathologic PI (see Table, Supplemental Digital Content 1, http://links.lww.com/TA/A892) highlight the importance of our key predictive indicators of hemoglobin, lactate 2 mmol/L or greater, INR, and the presence of small bowel PI. For example, in a patient presenting with a normal hemoglobin of 14 g/dL, lactate less than 2 mmol/L, a normal INR (1.0), and non–small bowel PI, the probability of pathologic PI was only 3%. In contrast, the presence of small bowel PI increases the probability to 9%. Furthermore, if lactate 2 mmol/L or greater is present plus small bowel PI, the risk of pathologic PI rises to 35%. As the INR increases to 2.0, the risk of pathologic PI almost doubles to 65%. Likewise, with a normal INR, normal lactate, and non–small bowel PI, the conditional probability of pathologic PI rises to 4% for hemoglobin of 13 g/dL, 6% for 12 g/dL, 8% for 11 g/dL, and 11% for 10 g/dL. With the addition of lactate 2 mmol/L or greater, normal INR, and presence of small bowel PI, the conditional probabilities increase to 44%, 53%, 62%, and 70% for the respective hemoglobin drops from 13 g/dL to 10g/dL, respectively. Additional combinations of key indicators for differing hemoglobin concentrations and INRs, presence of lactate of 2 mmol/L or greater, and location of pneumatosis are provided in Supplemental Digital Content 1, http://links.lww.com/TA/A892 to estimate conditional probabilities of pathologic PI.

Limitations

This was a prospective observational study. No interventions were performed in these patents secondary to the study, but rather patients underwent surgery if the clinical judgment of the physicians involved indicated they needed such interventions. Missing data were present in 47 of the 127 patients precluding their inclusion in the logistic regression modeling. Those with missing data were compared with those not missing data, and there was no statistically significant difference in demographics, initial presentation, or mortality. Thus, the data are missing at random. In the subset analysis that included only those patients presenting initially without peritonitis on physical examination, a lactate value of 2.0 mmol/L or greater, elevated INR, and decreased hemoglobin all trended toward statistical significance for prediction of pathologic PI, but did not meet the $p < 0.05$ level when nesting for center effect. We believe this reflects

TABLE 6. Comparison of the Independent Predictors of Pathologic PI Between Models Including and Not Including Patients Presenting With Peritonitis Controlled for Center Effect

	All Patients Including Peritonitis as Predictor Variable*		All Patients Excluding Peritonitis as Predictor Variable		Subset Presenting Without Peritonitis	
Predictor Variable	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Lactate ≥2 mmol/L	5.0 (1.1–22.4)	0.037	5.0 (1.5–17.0)	0.009	10.1 (0.9–115)	0.055
Elevated INR	4.1 (1.2–13.9)	0.023	2.9 (1.1–7.3)	0.030	7.6 (0.9–66.8)	0.066
Hemoglobin	0.7 (0.5–0.9)	0.023	0.7 (1.1–1.9)	0.012	0.7 (0.4–1.0)	0.063
Peritonitis	35.8 (3.0–407)	0.005				
AUROC (95% CI)	0.924 (0.866–0.982)		0.852 (0.764–0.939)		0.873 (0.792–0.953)	

*Model also includes small bowel pneumatosis, acute kidney injury, and ascites on CT imaging.
AUROC, area under the receiver operating curve; CI, confidence interval.

the study being underpowered for this subset analysis when center effect is accounted for.

Future Investigation

Perhaps future efforts can be directed to clarifying within the group of pathologic PI, of which they can undergo nonoperative treatment while receiving aggressive resuscitation on an attempt to reverse the ischemia process and avoid transmural necrosis.

CONCLUSIONS

We recommend surgical exploration to be strongly considered for those PI patients presenting also with a lactate 2 mmol/L or greater and/or peritonitis. We suggest careful clinical correlation in those patients with small bowel PI, adynamic ileus, anemia, and high INR.

Pathologic PI is associated most strongly with a decreased hemoglobin, elevated INR, and lactate of 2 mmol/L or greater even in patients presenting without peritonitis. We recommend a high index of suspicion of disease requiring operative intervention in patients demonstrating these initial laboratory abnormalities especially when radiographic findings including small bowel PI and ascites are also present.

AUTHORSHIP

P.F. and J.D. conceived the study. P.F. recruited the principal investigators for all centers and built the database in REDCAPs. R.C. performed all statistical analysis. P.F. and R.C. wrote the manuscript. All authors contributed to the data for the study and contributed with critical editing of the present article.

ACKNOWLEDGMENT

The authors thank Lindsay O'Meara, CRNP, and Dr Andrew Young who helped in data collection for this project.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. DuBose JJ, Lissauer M, Maung AA, Piper GL, O'Callaghan TA, Luo-Owen X, Inaba K, Okoye O, Shestopalov A, Fielder WD, et al. Pneumatosis Intestinalis Predictive Evaluation Study (PIPES): a multicenter epidemiologic study of the Eastern Association for the Surgery of Trauma. *J Trauma Acute Care Surg*. 2013;75(1):15–23.
2. Barmase M, Kang M, Wig J, Kochhar R, Gupta R, Khandelwal N. Role of multidetector CT angiography in the evaluation of suspected mesenteric ischemia. *Eur J Radiol*. 2011;80(3):e582–e587.
3. Duron VP, Rutigliano S, Machan JT, Dupuy DE, Mazzaglia PJ. Computed tomographic diagnosis of pneumatosis intestinalis: clinical measures predictive of the need for surgical intervention. *Arch Surg*. 2011; 146(5):506–510.
4. Pickhardt PJ, Kim DH, Taylor AJ. Asymptomatic pneumatosis at CT colonography: a benign self-limited imaging finding distinct from perforation. *AJR Am J Roentgenol*. 2008;190(2):W112–W117.
5. Honne K, Maruyama A, Onishi S, Nagashima T, Minota S. Simultaneous pneumatosis cystoides intestinalis and pneumomediastinum in a patient with systemic sclerosis. *J Rheumatol*. 2010;37(10):2194–2195.
6. Marinello DK, Rafael D, Paiva Edos S, Dominoni RL. Systemic lupus erythematosus complicated by intestinal vasculitis and pneumatosis intestinalis. *Rev Bras Reumatol*. 2010;50(5):596–602.
7. Op de Beeck B, Peters K, Spinhoven MJ, Snoeckx A, Salgado R, Parizel PM. Asymptomatic pneumatosis intestinalis in AIDS. *JBR-BTR*. 2009;92(5):253–255.
8. Gelman SF, Brandt LJ. Pneumatosis intestinalis and AIDS: a case report and review of the literature. *Am J Gastroenterol*. 1998;93(4):646–650.
9. Grimm JC, Berger JC, Lipsett PA, Haut ER, Ferrada P. A case of profound pneumatosis intestinalis in a patient with recent polytrauma. *J Trauma Acute Care Surg*. 2015;78(1):209–210.
10. Kreiss C, Forohar F, Smithline AE, Brandt LJ. Pneumatosis intestinalis complicating *C. difficile* pseudomembranous colitis. *Am J Gastroenterol*. 1999; 94(9):2560–2561.
11. Matsumoto A, Isomoto H, Shikuwa S, Okamoto K, Yamaguchi N, Ohnita K, Mizuta Y, Fujii M, Kohno S. Pneumatosis intestinalis in ulcerative colitis. *Med Sci Monit*. 2009;15(9):CS139–CS142.
12. Vijayakanthan N, Dhamanaskar K, Stewart L, Connolly J, Leber B, Walker I, Trus M. A review of pneumatosis intestinalis in the setting of systemic cancer treatments, including tyrosine kinase inhibitors. *Can Assoc Radiol J*. 2012; 63(4):312–317.
13. Wiesner W, Mortelé KJ, Glickman JN, Ji H, Ros PR. Pneumatosis intestinalis and portomesenteric venous gas in intestinal ischemia: correlation of CT findings with severity of ischemia and clinical outcome. *AJR Am J Roentgenol*. 2001;177(6):1319–1323.
14. Tsai YM, Hsu KF, Yu JC, Chan DC, Liu YC. Life-threatening signs of ischemic bowel disease-portomesenteric venous gas. *J Trauma*. 2011;71(1):E18.
15. Ho LM, Paulson EK, Thompson WM. Pneumatosis intestinalis in the adult: benign to life-threatening causes. *AJR Am J Roentgenol*. 2007;188(6):1604–1613.
16. Saito M, Tanikawa A, Nakasute K, Tanaka M, Nishikawa T. Additive contribution of multiple factors in the development of pneumatosis intestinalis: a case report and review of the literature. *Clin Rheumatol*. 2007;26(4):601–603.
17. St Peter SD, Abbas MA, Kelly KA. The spectrum of pneumatosis intestinalis. *Arch Surg*. 2003;138(1):68–75.
18. Woo K, Major K, Kohanzadeh S, Allins AD. Laparotomy for visceral ischemia and gangrene. *Am Surg*. 2007;73(10):1006–1008.
19. Hepgur M, Ahluwalia MS, Anne N, Thomas J, Liu H, Schiff MD, Loud PA, Hahn TE, Bullard Dunn KM, McCarthy PL Jr. Medical management of pneumatosis intestinalis in patients undergoing allogeneic blood and marrow transplantation. *Bone Marrow Transplant*. 2011;46(6):876–879.
20. Saracco P, Vitale P, Scolfaro C, Pollio B, Pagliarino M, Timeus F. The coagulopathy in sepsis: significance and implications for treatment. *Pediatr Rep*. 2011;3(4):e30.
21. Hawn MT, Canon CL, Lockhart ME, Gonzalez QH, Shore G, Bondora A, Vickers SM. Serum lactic acid determines the outcomes of CT diagnosis of pneumatosis of the gastrointestinal tract. *Am Surg*. 2004;70(1):19–23; discussion 23–4.
22. Wayne E, Ough M, Wu A, Liao J, Andresen KJ, Kuehn D, Wilkinson N. Management algorithm for pneumatosis intestinalis and portal venous gas: treatment and outcome of 88 consecutive cases. *J Gastrointest Surg*. 2010; 14(3):437–448.

DISCUSSION

Dr. Fred A. Luchette (Maywood, Illinois): Good morning, everyone. Dr. Davis, never look down. I'll begin by congratulating Dr. Callcut and her colleagues on completing this prospective clinical study.

This is an interesting study in that the authors correlated the finding of pneumatosis cystoides intestinalis on CT scan with clinical and laboratory findings to predict patients that will have transmural ischemia at laparotomy. They conclude that peritonitis and an elevated lactic acid are predictive of dead bowel. I don't know about the rest of the audience, but I think we have known this for a long time.

I do want to remind everyone that pneumatosis intestinalis is not a disease but merely a radiographic sign that can be idiopathic or associated with many intestinal or nonintestinal disorders such as obstructive pulmonary disease and asthma. However, most cases of pneumatosis intestinalis are secondary to bowel ischemia and/or infarction and only 15% are idiopathic. With that in mind, I am not sure why the group labeled the patients that

were managed non-operatively as "benign PI" since pneumatosis is a radiographic sign of an underlying problem. So Rachael, perhaps you could begin by commenting on why this label was applied to the non-operative group. I do have a couple more questions for the authors.

If we agree that mesenteric ischemia is the most common etiology for pneumatosis, I think that your group missed an opportunity to also correlate the vascular anatomy on the CT images with the other study variables. Specifically, knowing if the etiology of ischemia is due to an embolism, venous thrombosis or acute on chronic thrombosis will allow you to plan for the proper operation in advance. So Rachael, I would appreciate hearing your comments regarding not including this important information that can be gleaned from the CT images.

Sixty-two percent of the patients in the Benign PI group did not receive a laparotomy. How can you be so certain that the ischemia didn't involve more than the mucosa? Did you follow these patients long term to see if they developed an ischemic stricture or stensosis? Similarly, five patients in the pathologic PI group did not undergo laparotomy. How did you determine that they indeed had transmural necrosis? The range of days for hospital admission in the Benign PI group begins at zero days. This would suggest that the patient was discharged after the CT scan. How can you be certain that the patient did not have ischemic bowel? Why would an outpatient be included in your study population?

Lastly, I need your help with how I am to change my practice as a result of your findings in this study. Recently the residents at Loyola have named me the Old Dog and I am not sure why. For several decades, I have relied on the patient's history and clinical exam to decide if they need an operation. So when I have a patient with peritonitis and an elevated lactate, the presence or absence of pneumatosis cystoides intestinalis on a CT scan will not deter me from proceeding to the OR emergently. However, as I noted above, it will cause me to pay particular attention to the vasculature for an etiology. In contrast, when the medicine service obtains a CT scan on Friday at 5:00pm for whatever ridiculous reason and they consult us because there is mesenteric venous gas, we do not immediately schedule the patient for a laparotomy unless there is peritonitis. If the abdominal exam is benign, I would begin the patient on broad spectrum antibiotics, resuscitate them and follow them with serial exams. So with the conclusions that you presented today, how should I change my practice?

I, again, want to congratulate you and your team for an excellent study and presentation. And I also want to thank the Program Committee for allowing this Old Dog the privilege of opening the discussion of this interesting study. Thank you.

Dr. Sheldon H. Teperman (New York, New York): Rachael, I'm particularly grateful to you for doing this study. I used to have an old boss, that on morning report if you hadn't operated on every patient with pneumatosis he would tear your head off.

My question is, since you so elegantly elucidated that there are the benign causes in 79% of patients, was your dataset able to actually capture it if it wasn't bad bowel or dead bowel. What were the causes of the benign cases of pneumatosis in your study?

Dr. Ajai K. Malhotra (Burlington, Vermont): I enjoyed the presentation. The problem has come about by increasing use of CT scan and we get these patients which have pneumatosis and the patient feels fine and then what do you do.

Well, I suspect we can go back to what Past-President Dr. Richardson had presented a paper in the early '80s, do a DPL. DPL in non-trauma acute abdomens is extremely sensitive to presence or absence of trans-mural necrosis because in the presence of trans-mural necrosis there will be leukosequestration.

The second point, just as Fred said, just because the feeling was that the pneumatosis did not contribute to the death in the so-called benign ones does not mean it did not. There was some problem that probably contributed to the death, even if it was not transmural necrosis, in the labeled but not benign ones.

Dr. Charles E. Wiles, III (Buffalo, New York): At the Medical Society for the State of New York House of Delegates' meeting last spring, a family practice intern from an institution both Dr. Luchette and I have been associated with at various times presented a paper which won honorable mention stating that you could identify in the emergency department 75% of the benign PI patients and discharge them home.

The reason it didn't win first prize is the surgeon on the jury thought that that might be a rash approach. I'd ask the authors to comment.

Dr. Kevin M. Schuster (New Haven, Connecticut): Very nicely presented. I just have one simple question. I wonder about how these patients presented because I think about these patients differently. The patient that presents to the emergency department with new onset A-FIB and acute abdominal pain is different from the patient who has been in the medical intensive care unit for three months and gets a CT scan just because the patient had a fever and pneumatosis is discovered.

Dr. Victoria Sharp (Fresno, California): Really interesting paper. I just had a question about the INR and hemoglobin that you mentioned. Did you have specific values that you used as your elevated INR or hemoglobin? Were those, especially the hemoglobin, gender-specific that you used? Thank you.

Dr. Rachael A. Callcut (San Francisco, California): First, I'd like to thank Dr. Luchette for his very important comments, in which he appropriately highlighted the difficulty in doing this type of study, and thank all the other folks who got up to ask questions.

First I want to address the questions that were asked and then I'll address Dr. Luchette's concerns.

With regard to the causes of benign pneumatosis, we were able to determine based on final diagnoses that were presented to us or autopsy findings in none of those patients did they die of a septic cause of death. The vast majority of these patients died of unrelated things such as cancers that were unrelated to the abdomen.

With regard to Dr. Malhotra and the issue of the DPL and the deaths, it is interesting that some of the patients who were in the benign group actually did go to the operating room and got as close as we do to DPLs now and had diagnostic laparoscopies and they were closed immediately. So it is somewhat analogous to the DPLs situation.

With regard to the paper that was presented at another society with the benign pneumatosis with the rate of 75% of

the patients that were—you see that is very close to what we have here. And it's likely that benign pneumatosis is actually much more common than we have traditionally thought about. I don't, however, think that our data is strong enough to actually recommend that you can determine upfront that these patients are clearly benign.

Of the patients who were in the benign group who ultimately did have operations, there were findings in those groups not related to the pneumatosis—not directly related to bowel ischemia, I should say—but the pneumatosis was related to other conditions such as bowel cancers that were diagnosed at the time of laparotomy. So I'm not certain that we can establish that those patients can just safely be discharged home based on our data.

We did not collect how the patients presented and that would be a very interesting finding. We can go back and look at it. But we do know the length of time from when the patients had their CT scan done and the labs done before that and they were generally two to four hours. I think we can safely say that something acutely had changed about those patients in the immediate preceding time to the CT scans being obtained because labs were obtained in a relatively short time period—two to four hours before.

We did not use a specific cut-off and we treated hemoglobin and INR as continuous variables. But just to remind folks, the hemoglobin in the group that had the pathologic pneumatosis was around 10 versus around 12 in the benign group. And INR was 1.1 in the benign group and 1.4 in those with pathologic pneumatosis.

Dr. Luchette has pointed out some really important features. And we have made some amendments to our paper to do the sensitivity analysis to look at this data as I presented, not just in those who have peritonitis but those who do not have peritonitis.

It would have been great for us to be able to look at the modality of imaging and correlate it to the specific vascular changes; however, as you can imagine because of the way that we set up the study the patients already had their CT scan before they were actually enrolled into the study so not everyone had a CT angio which is, of course, the gold standard in assessing the vasculature so it is very difficult with low numbers to be able to actually say something meaningful about that.

We do not have long-term data on the patients so it's a fair criticism that we don't know other than based on the clinical diagnostic modalities that were used, including some scopes in the patients, it was not possible for us to determine whether or not these patients have had long-term complications of their benign pneumatosis.

Again, I'd like to thank the AAST and the Multi-Institutional Trials Committee as well as my coauthors. Thank you.