Pneumatosis Intestinalis Predictive Evaluation Study (PIPES): A multicenter epidemiologic study of the Eastern Association for the Surgery of Trauma

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BACKGROUND: Pneumatosis intestinalis (PI) is associated with numerous adult conditions, ranging from benign to life threatening. To date, series of PI outcomes consist of case reports and small retrospective series.

METHODS: We conducted a retrospective multicenter study, involving eight centers, of PI from January 2001 to December 2010. Demographics, medical history, clinical presentation, and outcomes were collected. Primary outcome was the presence of pathologic PI defined as confirmed transmural ischemia at surgery or the withdrawal of clinical care and subsequent mortality. Forward logistic regression and a regression tree analysis was used to generate a clinical prediction rule for pathologic PI.

RESULTS: During the 10-year study period, 500 patients with PI were identified. Of this number, 299 (60%) had benign disease, and 201 (40%) had pathologic PI. A wide variety of variables were statistically significant predictors of pathologic PI on univariate comparison. In the regression model, a lactate of 2.0 or greater was the strongest independent predictor of pathologic PI, with hypotension or vasopressor need, peritonitis, acute renal failure, active mechanical ventilation, and absent bowel sounds also demonstrating significance. Classification and regression tree analysis was used to create a clinical prediction rule. In this tree, the presence of a lactate value of 2.0 or greater and hypotension/vasopressor use had a predictive probability of 93.2%.

CONCLUSION: Discerning the clinical significance of PI remains a challenge. We identified the independent predictors of pathologic PI in the largest population to date and developed of a basic predictive model for clinical use. Prospective validation is warranted. (*J Trauma Acute Care Surg*. 2013;75: 15–23. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Epidemiologic study, level III.

KEY WORDS: Pneumatosis intestinalis; computed tomography; lactate.

Pneumatosis intestinalis (PI) or the finding of gas within the bowel wall on abdominal imaging may be associated with numerous conditions in the adult, ranging from benign to life threatening. The true incidence of PI is unknown, but the expanded use of computed tomography (CT) imaging may be increasing the detection of this radiographic finding.

The causes of PI may be multifactorial. This finding has been associated with a wide variety of pathologies including acquired immunodeficiency,[1,2] transplant status,[3–5] cancer treatment,[6] scleroderma,[7,8] cystic fibrosis,[9] systemic lupus,[10,11] inflammatory bowel disease,[12,13] colitis,[14] intestinal ischemia or vascular occlusion,[15–17] and trauma[18–21] and even bowel preparation[22] or specific procedures.[23] Across this wide disparity in potential causative mechanisms, the ability to definitively determine if PI is benign or pathologic requiring surgical intervention has not been well defined.

Our present study is a multicenter retrospective evaluation of patients with PI as a radiographic finding. To the best of our understanding, it is the largest such study to date. It is our hope that by correlating PI with collected elements of patient history, examination, laboratory findings, and outcome, we will improve the ability to predict the need for surgical intervention after identification of this radiographic finding.

PATIENTS AND METHODS

This was a retrospective multicenter study conducted under the sponsorship of the Eastern Association for the Surgery of Trauma. The study protocol was approved by the Eastern Association for the Surgery of Trauma Multi-Institution Trials Committee, and each participating center obtained approval from its institutional review board. Patients with the identification of PI or gas in the bowel wall by a staff radiologist via either plain radiography or CT during a 10-year period from January 2001 to December 2010 were included in the analysis. Extensive patient data composing of demographics, medical history, clinical presentation, and outcomes were collected using a standardized data collection sheet. The primary outcome was the presence of pathologic PI defined as either transmural ischemia detected at endoscopy/surgery or the withdrawal of clinical care and subsequent mortality in the setting of PI. Secondary outcomes studied were mortality, ventilator

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days, as well as intensive care unit and hospital length of stay. Infectious complications as defined by the available hospital registry data were also included, as were laboratory values at the time of PI diagnosis (for lactated and all other laboratory values, the closest value to the precise time of CT diagnosis was used—not to exceed 6 hours before or after obtaining CT).

Demographic and clinical characteristics between patients who developed pathologic PI and those who did not were compared. Univariate analyses were performed using the χ^2 test with Yates correction for comparison of proportions and the Student's *t* test or the Mann-Whitney U-test for comparison of continuous variables. If any cell contained five patients or less, the two-sided Fisher's exact test was used. To identify factors independently associated with the development of pathologic PI, all potential risk factors that were significant at $p < 0.2$ were entered into a forward logistic regression model. Adjusted odds ratio and 95% confidence intervals were derived. Variables from this model were entered into a classification and regression tree (CART) to generate a clinical prediction rule for pathologic PI.

Data were analyzed using SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

During the 10-year study period, 500 patients with PI were included from eight centers in the United States. The number of patients contributed varied by center from 15 to 137, with 7 of 8 centers contributing at least 30 patients each.

TABLE 1. Demographic Details and Clinical History

	All Patients (n = 500)	Benign (n = 299)	Pathologic (n = 201)	*p*
Age, y	56.6 ± 19.4	53.3 ± 19.3	61.4 ± 18.7	<0.001
Age ≥ 60 y	229/498 (46.0%)	116/297 (39.1%)	113/201 (56.2%)	<0.001
Sex, male	283/500 (56.6%)	173/299 (57.9%)	110/201 (54.2%)	0.398
Hospital day of diagnosis	8.2 ± 15.5	7.6 ± 15.2	9.1 ± 15.8	0.299
Medical history				
Respiratory conditions				
Asthma	25/500 (5.0%)	12/299 (4.0%)	13/201 (6.5%)	0.217
Bronchitis	19/500 (3.8%)	11/299 (3.7%)	8/201 (4.0%)	0.863
Emphysema	24/500 (4.8%)	16/299 (5.4%)	8/201 (4.0%)	0.482
Pulmonary fibrosis	6/500 (1.2%)	6/299 (2.0%)	0/201 (0%)	0.086
Cystic fibrosis	1/500 (0.2%)	1/299 (0.3%)	0/201 (0.0%)	1.000
Bowel conditions				
Adynamic ileus	8/500 (1.6%)	5/299 (1.7%)	3/201 (1.5%)	1.000
Inflammatory bowel disease	9/500 (1.8%)	7/299 (2.3%)	2/201 (1.0%)	0.325
Pseudo-obstruction	9/500 (1.8%)	3/299 (1.0%)	6/201 (3.0%)	0.167
Ulcerative colitis	8/500 (1.6%)	7/299 (2.3%)	1/201 (0.5%)	0.152
Crohn's disease	10/500 (2.0%)	8/299 (2.7%)	2/201 (1.0%)	0.329
Enteritis	4/500 (0.8%)	0/299 (0.0%)	4/201 (2.0%)	0.026
Peptic ulcer disease	18/500 (3.6%)	11/299 (3.7%)	7/201 (3.5%)	0.908
Bowel obstruction	41/500 (8.2%)	25/299 (8.4%)	16/201 (8.0%)	0.873
Diverticulitis	18/500 (3.6%)	12/299 (4.0%)	6/201 (3.0%)	0.545
Surgical history				
Recent endoscopy	57/500 (11.4%)	37/299 (12.4%)	20/201 (10.0%)	0.403
Recent laparoscopy	13/500 (2.6%)	9/299 (3.0%)	4/201 (2.0%)	0.482
Recent abdominal surgery	80/500 (16.0%)	52/299 (17.4%)	28/201 (13.9%)	0.301
Medication use				
Corticosteroids	72/500 (14.4%)	36/299 (12.0%)	36/201 (17.9%)	0.067
Chemotherapeutic agent use	57/500 (11.4%)	40/299 (13.4%)	17/201 (8.5%)	0.090
Lactulose	34/500 (6.8%)	15/299 (5.0%)	19/201 (9.5%)	0.053
Systemic conditions				
Scleroderma	6/500 (1.2%)	5/299 (1.7%)	1/201 (0.5%)	0.409
Systemic lupus	6/500 (1.2%)	4/299 (1.3%)	2/201 (1.0%)	0.730
HIV/AIDS	12/500 (2.4%)	7/299 (2.3%)	5/201 (2.5%)	1.000
Leukemia	13/500 (2.6%)	11/299 (3.7%)	2/201 (1.0%)	0.085
Chronic renal failure	62/500 (12.4%)	24/299 (8.0%)	38/201 (18.9%)	<0.001
History of organ transplant	36/500 (7.2%)	18/299 (6.0%)	18/201 (9.0%)	0.221
History of malignancy	120/500 (24.0%)	76/299 (25.4%)	44/201 (21.9%)	0.365

AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Mean diagnosis of PI was hospital Day 8. Of this number, 299 (60%) had benign disease, and the remaining 201 (40%) had pathologic PI. The mean age was 56.6 ± 19.4 years, with 46% of patients 60 years or older and 57% being of male sex. Patients with pathologic disease were more likely to be older (61 ± 18 years vs. 53 ± 19 years, $p < 0.001$), with a history of enteritis and chronic renal failure (Table 1).

The most common clinical sign on presentation was abdominal distension (54%), followed by constipation (19%) and peritonitis (17%). One hundred three patients (21%) however could not be properly evaluated at the time of diagnosis either owing to sedation or altered mental status. Of the clinical findings collected, abdominal distension (67% vs. 45%, $p < 0.001$) peritonitis (29% vs. 10%), absent bowel sounds (21% vs. 7%, $p < 0.001$), and abdominal rigidity (14% vs. 5%, $p < 0.001$) were significantly associated with pathologic PI. The presence of diarrhea was associated significantly with benign disease (11% vs. 19%, $p < 0.001$).

The use of antibiotics (65% vs. 43%, $p < 0.001$), steroids (26% vs. 14%, $p = 0.001$), and mechanical ventilation (37% vs. 4%, $p < 0.001$) were significantly associated with pathologic PI. Concurrent pneumonia (11% vs. 5%, $p = 0.017$), blood stream infections (10% vs. 4%, $p = 0.017$), hypotension/vasopressor use (41% vs. 4%, $p < 0.001$), acute renal failure (38% vs. 10%, $p < 0.001$), sepsis (28% vs. 5%, $p < 0.001$), acute lung injury (12% vs. 2%, $p < 0.001$), and multiorgan failure (12% vs. 1%, $p < 0.001$) were also associated with pathologic disease (Table 2).

Elevations in white blood count (16 ± 11 vs. 12 ± 7, $p < 0.001$), potassium (4 ± 3 vs. 4. ± 1, $p < 0.001$), blood urea nitrogen of greater than 20 mg/dL (78% vs. 46%, $p < 0.001$), elevated creatinine (2.3 ± 2.2 vs. 1.3 ± 1.2, $p < 0.001$), lactate of greater than 2.0 (67% vs. 18%, $p < 0.001$), abnormal coagulation indices (activated thromboplastin time and international normalized ratio), bilirubin, and transaminases were all significantly associated with pathologic PI on univariate analysis. Platelet count was, in contrast, significantly lower than in benign disease (Table 3).

Computed tomography (CT) imaging was used in the identification of 96% of cases. The large bowel disease was the most common site for PI, but jejunal (36% vs. 27%, $p = 0.023$) and ileal (43% vs. 22%, $p < 0.001$) pneumatosis locations were most commonly associated with pathologic PI. The presence of diffuse, extensive intramural bowel air (19% vs.

TABLE 2. Clinical Presentation

	All Patients (n = 500), n (%)	Benign (n = 299), n (%)	Pathologic (n = 201), n (%)	*p*
Presentation				
Distension	268/500 (53.8)	134/299 (45.0)	134/201 (67.0)	<0.001
Absent bowel sounds	61/500 (12.2)	20/299 (6.7)	41/201 (20.5)	<0.001
High pitched bowel sounds	17/499 (3.4)	13/299 (4.3)	4/200 (2.0)	0.210
Peritonitis	86/500 (17.2)	29/299 (9.7)	57/201 (28.5)	<0.001
Abdominal rigidity	45/500 (9.0)	16/299 (5.4)	29/201 (14.4)	<0.001
Heme-positive stool	47/499 (9.4)	26/299 (8.7)	21/200 (10.5)	0.499
Diarrhea	79/499 (15.8)	57/299 (19.1)	22/200 (11.0)	0.016
Constipation	97/499 (19.4)	59/299 (19.7)	38/200 (19.0)	0.839
Compromised evaluation	103/500 (20.6)	36/299 (12.0)	67/201 (33.3)	<0.001
Management at time of diagnosis				
Antibiotic use	257/498 (51.6)	127/297 (42.8)	130/201 (64.7)	<0.001
Current steroid use	93/499 (18.6)	42/299 (14.0)	51/200 (25.5)	0.001
Current chemotherapy use	23/500 (4.6)	13/299 (4.3)	10/201 (5.0)	0.829
Mechanical ventilation	86/500 (17.2)	12/299 (4.0)	74/201 (36.8)	<0.001
Associated infections				
Any active infection	143/500 (28.6)	78/299 (26.1)	65/201 (32.3)	0.132
Pneumonia or VAP	39/500 (7.8)	16/299 (5.4)	23/201 (11.4)	0.017
Blood stream infection	33/500 (6.6)	13/299 (4.3)	20/201 (10.0)	0.017
Clostridium difficile colitis	20/500 (4.0)	12/299 (4.0)	8/201 (4.0)	1.000
Other colitis	9/500 (1.8)	5/299 (1.7)	4/201 (2.0)	1.000
UTI	22/500 (4.4)	13/299 (4.3)	9/201 (4.5)	1.000
Other infection	53/500 (10.6)	35/299 (11.7)	18/201 (9.0)	0.375
Complications on presentation				
Hypotension or vasopressor use	95/500 (19.0)	13/299 (4.3)	82/201 (40.8)	<0.001
Acute renal failure	107/500 (21.4)	30/299 (10.0)	77/201 (38.3)	<0.001
Hepatic failure	30/500 (6.0)	10/299 (3.3)	20/201 (10.0)	0.375
Sepsis	73/500 (14.6)	16/299 (5.4)	57/201 (28.4)	<0.001
Acute lung injury	30/500 (6.0)	5/299 (1.7)	25/201 (12.4)	<0.001
Multiorgan failure	26/499 (5.2)	2/298 (0.7)	24/201 (11.9)	<0.001

UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

TABLE 3. Laboratory Findings

Laboratory Findings	All Patients (n = 500)	Benign (n = 299)	Pathologic (n = 201)	*p*
WCC	13.9 ± 9.2	12.2 ± 7.2	16.2 ± 11.1	<0.001
WCC < 5 or >11, $\times 10^3/\mu L$	306/476 (64.3%)	162/280 (57.9%)	144/196 (73.5%)	<0.001
Hematocrit, %	35.1 ± 13.3	35.6 ± 7.9	34.3 ± 18.4	0.31
Platelet, $\times 100{,}000/\mu L$	272.8 ± 154.3	295.6 ± 153.2	238.9 ± 150.1	<0.001
Sodium	137.3 ± 8.8	137.3 ± 6.3	137.2 ± 11.4	0.866
Chloride	102.0 ± 12.1	101.8 ± 11.3	102.4 ± 13.2	0.57
Potassium	4.2 ± 2.3	4.0 ± 1.5	4.6 ± 3.1	0.002
Bicarbonate	22.3 ± 5.4	23.6 ± 4.8	20.6 ± 5.8	<0.001
BUN	32.4 ± 25.6	24.1 ± 19.0	44.0 ± 29.1	<0.001
BUN > 20 mg/dL	273/462 (59.1%)	124/270 (45.9%)	149/192 (77.6%)	<0.001
Creatinine	1.7 ± 1.8	1.3 ± 1.2	2.3 ± 2.2	<0.001
Creatinine > 2.0	118/464 (25.4%)	36/271 (13.3%)	82/193 (42.5%)	<0.001
pH	7.34 ± 0.24	7.36 ± 0.39	7.33 ± 0.12	0.501
P_{O_2}	127.6 ± 88.2	110.9 ± 62.6	135.9 ± 94.8	0.071
P_{CO_2}	36.4 ± 11.0	36.2 ± 12.4	36.9 ± 7.6	0.675
Base deficit	−3.4 ± 7.3	−4.7 ± 7.7	−0.7 ± 5.3	0.001
Lactate	3.0 ± 3.9	1.6 ± 1.3	4.1 ± 4.9	<0.001
Lactate > 2.0	118/270 (43.7%)	22/126 (17.5%)	96/144 (66.7%)	<0.001
PTT	35.0 ± 16.8	31.0 ± 9.1	38.8 ± 21.1	<0.001
INR	1.7 ± 2.2	1.4 ± 1.1	2.1 ± 2.8	0.006
Total bilirubin	2.0 ± 5.1	1.3 ± 3.5	3.0 ± 6.4	0.013
Direct bilirubin	1.2 ± 3.6	0.6 ± 1.3	2.0 ± 5.4	0.005
Indirect bilirubin	0.8 ± 2.0	0.6 ± 0.7	1.1 ± 3.2	0.173
AST; mean ± SEM	231.8 ± 45.7	64.6 ± 18.5	475.0 ± 105.7	<0.001
ALT; mean ± SEM	127.7 ± 26.4	63.0 ± 22.1	225.0 ± 56.1	0.002

*WCC, white blood cell count; BUN, blood urea nitrogen; PTT, activated thromboplastin time; INR, international normalized ratio; AST, aspartate transaminase; ALT, alanine transaminase.

6%, $p < 0.001$), ascites (54% vs. 27%, $p < 0.001$), arteriovenous mesenteric occlusion (5% vs. 1%, $p = 0.002$), and vascular gas patterns (either hepatic portal or portomesenteric) (37% vs. 15%, $p < 0.001$) were also significantly associated with a diagnosis of pathologic PI.

Overall, surgery was performed in 199 patients (40% of cases). Surgical intervention for pathologic PI was conducted in 118 (59%) of pathologic PI cases, with the remaining 83 cases ultimately undergoing withdrawal of care and subsequent mortality (Table 4).

Variables differing at $p < 0.2$ in the univariate analysis were entered into a stepwise forward logistic regression model to identify independent risk factors for pathologic PI. Candidate variables with more than 50% missing data were excluded from the analysis. In the regression model, a lactate of 2.0 or greater was the strongest independent predictor of pathologic PI. Other variables included in the model were hypotension or vasopressor use, peritonitis, acute renal failure, active mechanical ventilation, and absent bowel sounds (Table 5).

CART analysis using variables from the regression was used to create a clinical prediction rule (Fig. 1). Only three variables were considered in this tree (lactate, hypotension, and peritonitis). In this tree, the presence of a lactate value 2.0 or greater and hypotension/vasopressor use had a predictive probability of 93%, while the absence of all three variables was a weak predictor with a diagnostic accuracy of 22%.

DISCUSSION

PI in the adult remains a clinical challenge of care about which little is completely understood.[23–27] While several associated disease processes have been identified,[1–22] little is precisely understood about the specific pathophysiology accounting for this radiographic finding. A mechanical theory hypothesizes that gas dissects into the bowel wall from either the intestinal lumen or the lungs via the mediastinum owing to some mechanism causing increased overpressure (i.e., bowel obstruction or emphysema). A bacterial theory proposes that gas forming organisms enter the submucosa through mucosal rents or increased mucosal permeability and produce gas within the bowel wall.

While both theories may have some validity, the finding of PI itself continues to confound surgeons desiring to select the optimal therapy. Many patients can be observed without any aggressive intervention, while others clearly require surgery for resection of ischemic bowel due to pathologic PI. To determine the correct management option, providers are required to use all of the clinical information available to them;

TABLE 4. Radiologic Investigations Performed

	All Patients (n = 500), n (%)	Benign (n = 299), n (%)	Pathologic (n = 201), n (%)	*p*
Plain radiography	61/499 (12.2)	42/298 (14.1)	19/201 (9.5)	0.121
CT imaging	478/499 (95.8)	283/299 (94.6)	195/200 (97.5)	0.171
Segment of bowel involved				
Large bowel	285/500 (57.0)	175/299	110/201 (54.7)	0.400
Gastric	29/500 (5.8)	18/299 (6.0)	11/201 (5.5)	0.848
Rectal	13/500 (2.6)	10/299 (3.3)	3/201 (1.5)	0.202
Duodenum	42/499 (8.4)	24/298 (8.1)	18/201 (9.0)	0.744
Jejunum	152/499 (30.5)	79/298 (26.5)	73/201 (36.3)	0.023
Ileum	153/499 (30.7)	66/298 (22.1)	87/201 (43.3)	<0.001
Appendix	3/500 (0.6)	2/299 (0.7)	1/201 (0.5)	1.000
Pattern of pneumatosis				
Linear	155/500 (31.0)	103/299 (34.4)	52/201 (25.9)	0.042
Antimesenteric	35/500 (7.0)	25/299 (8.4)	10/201 (5.0)	0.157
Circumferential	176/500 (35.2)	95/299 (31.8)	81/201 (40.3)	0.056
Isolated foci of air	118/500 (23.6)	88/299 (29.4)	30/201 (14.9)	<0.001
Moderate air in isolated region	148/500 (29.6)	95/299 (31.8)	53/201 (26.4)	0.194
Moderate air in multiple segments	111/500 (22.2)	56/299 (18.7)	55/201 (27.4)	0.023
Extensive air, isolated region	51/500 (10.2)	33/299 (11.0)	18/201 (9.0)	0.547
Extensive air, diffusely	57/500 (11.4)	19/299 (6.4)	38/201 (18.9)	<0.001
Bowel wall thickening	151/500 (30.2)	87/299 (29.1)	64/201 (31.8)	0.512
Dilated bowel	282/500 (56.4)	167/299 (55.9)	115/201 (57.2)	0.763
Ascites	190/500 (38.0)	82/299 (27.4)	108/201 (53.7)	<0.001
Arteriovenous mesenteric occlusion	12/499 (2.4)	2/298 (0.7)	10/201 (5.0)	0.002
Vascular gas	119/500 (23.8)	44/299 (14.7)	75/201 (37.3)	<0.001
Hepatic portal gas	78/500 (15.6)	24/299 (8.0)	54/201 (26.9)	<0.001
Retroperitoneal air	32/500 (6.4)	21/299 (7.0)	11/201 (5.5)	0.578
Portomesenteric venous gas	86/500 (17.2)	30/299 (10.0)	56/201 (27.9)	<0.001
Free peritoneal gas	99/500 (19.8)	54/299 (18.1)	45/201 (22.4)	0.234
Endoscopic evaluation	44/500 (8.8)	30/299 (10.0)	14/201 (7.0)	0.263
Surgery performed	199/500 (39.8)	81/299 (27.1)	118/201 (58.7)	

including medical history, physical examination, laboratory findings, and the specifics of the radiographic presentation.

Physical examination remains a mainstay of initial evaluation because patients with peritoneal signs typically mandate operative exploration to rule out intestinal perforation or ischemia. Many of these patients are, however, either obtunded or sedated to levels that potentially compromise the ability to obtain an adequate examination. In these instances, the selection of optimal care must rely more heavily on other contributory means of evaluation.

In the absence of confirmed peritonitis, laboratory markers remain a mainstay element of the evaluation of the PI patient. A number of obtainable laboratory values may contribute significantly to the development of a clinical picture requiring abdominal exploration. One of the best studied of these values is that of serum lactate. In a retrospective study of 86 patients with findings of PI on CT of the abdomen, Hawn et al.[28] found that lactate values of greater than 2.0 mmol/L were significantly associated with a greater than 80% mortality in the setting of pathologic PI. The presence of hyperlactemia alone, however, may result from a number of causes unrelated to intestinal ischemia and is not of profound reliability in dictating the need for surgical intervention when considered in isolation. Regardless, hyperlactemia in the setting of PI is of significant concern. Our own results highlight that serum lactate values in excess of 2 mmol/L may be an independent predictor for the presence of pathologic PI in the setting of this radiographic finding.

It has been suggested that the specific radiographic characteristics of pneumatosis may be important in determining if identified PI is pathologic or benign in etiology. As CT imaging techniques and capabilities continue to evolve, greater granularity of assessment is now achievable.[29] Particularly in the setting of acute mesenteric ischemia, biphasic techniques may provide an improved ability to contribute to the need for subsequent operation.[30–32]

In one recent study by Barmase et al.,[29] investigators examined the use of multidetector CT angiography (MDCTA) among 31 patients with pneumatosis or other radiographic suspicion for defects in vascular perfusion. They found that MDCTA correctly diagnosed acute mesenteric ischemia with a sensitivity and specificity of 100%. The authors concluded that the use of MDCTA may prove of great utility in diagnosing one of the most common needs for surgical intervention in the setting of pathologic PI, that of acute mesenteric ischemia.

Another frequently associated radiographic finding that has been suggested to be of possible importance in the evaluation of PI is that of portal venous gas. Although the precise

TABLE 5. Independent Predictors of Pathologic Pneumatosis

Variable	Step	Odds Ratio (95% Confidence Interval)	*p*	*R*
Lactate > 2.0	1	4.3 (2.2–8.7)	<0.001	0.304
Hypotension or pressor use	2	5.1 (2.0–13.0)	0.001	0.097
Peritonitis	3	4.7 (2.2–10.3)	<0.001	0.053
Acute kidney injury	4	3.4 (1.5–7.8)	0.004	0.042
Active mechanical ventilation	5	3.3 (1.3–8.6)	0.013	0.018
Absent bowel sounds	6	2.8 (1.1–7.1)	0.034	0.015

Other variables in the model include older than 60 years, pseudo-obstruction, history of ulcerative colitis, use of corticosteroids, chemotherapeutic agents, lactulose, history of leukemia, chronic renal failure, abdominal distension, abdominal rigidity, diarrhea, compromised examination, use of antibiotics, current steroid use, active infections, pneumonia/ventilator-associated pneumonia, blood stream infections, sepsis, acute lung injury/adult respiratory distress syndrome, multiorgan failure, abnormal white blood cell count, creatinine greater than 2, jejunal PI, ileal PI, linear PI, antimesenteric PI, circumferential PI, isolated foci of air, moderate isolated region of air, moderate air in multiple segments, extensive air in diffuse segments, ascites, and vascular gas pattern.

mechanism behind this related radiographic entity has not been completely defined, the combination of portal venous air and PI has been examined by a number of authors in limited examinations.[32–37] In a study conducted by Weisner et al.,[36] investigators examined the outcomes of 23 patients with CT findings of pneumatosis in isolation or in combination with portal venous gas. The authors found that the combination of these findings was associated with a rate of transmural bowel infarction higher than the presence of isolated pneumatosis alone.

The location and degree of pneumatosis, in particular the number of affected enteric segments on CT imaging, may also be of importance in determining the need for surgical intervention for pathologic PI. Several studies have demonstrated higher rates of transmural ischemia and mortality in patients with pneumatosis of the small bowel.[36,37] In a report by Wayne et al.[37] of 88 consecutive cases of pneumatosis over 5 years at a single institution, the authors identified that patients with small bowel PI were significantly more likely to have evidence of pathologic PI owing to acute mesenteric ischemia that required subsequent resection.

In our present study, both the associated presence of portal venous air and the extent of pneumatosis seemed to be significantly associated with the finding of pathologic PI. Specifically, those patients who had their pneumatosis classified as "extensive air diffusely" were approximately three times more likely to have pathologic PI. In contrast, those with isolated regions of pneumatosis were more than twice as likely to have benign PI. Neither of these factors, however, proved to be independent predictors of pathologic PI on multivariate analysis.

The reality remains that a myriad of potential factors may serve as causative origins for PI, and no one element of evaluation is capable of discerning the need for surgical intervention. Only a limited number of groups, however, have engaged in multivariate analysis of pertinent variables in an effort to determine the independent risk factors for pathologic PI or the need for surgical intervention after the finding of PI. In the previously largest study of this kind, Duron et al.[38] examined 150 consecutive patients with CT imaged PI and noted that independent predictors for positive operative findings included abdominal distension (odds ratio, 13.19; $p = 0.01$), peritonitis (odds ratio, 9.35; $p = 0.07$), and lactic acidemia (odds ratio, 2.29; $p = 0.02$). Some of our present findings agree with those of this group, as we identified lactate greater

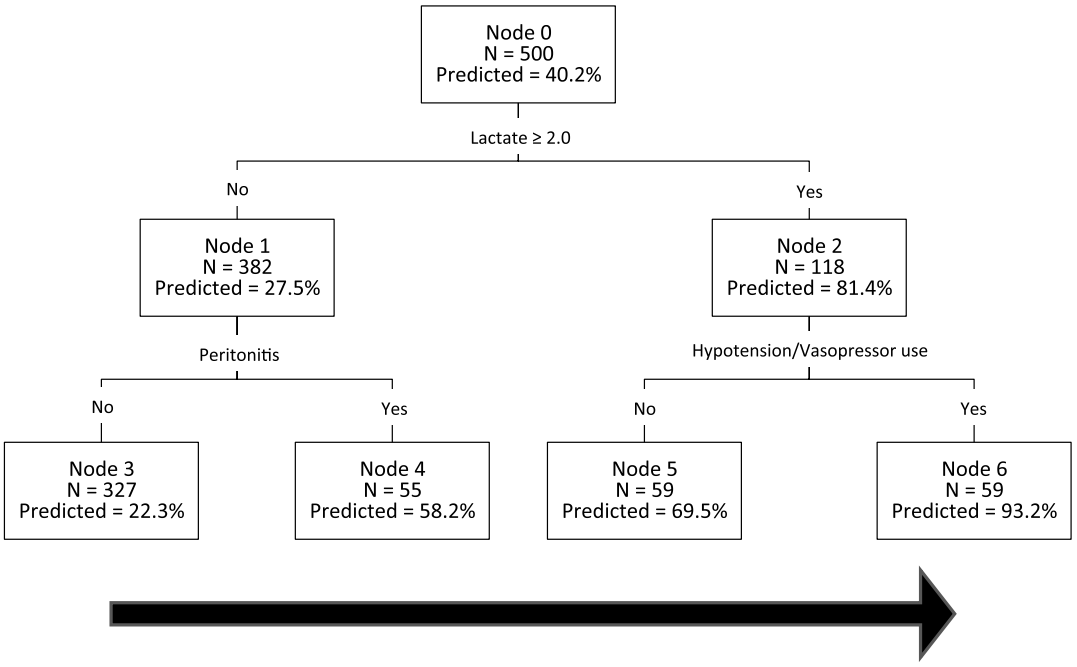

Figure 1. Tree model for prediction of pathologic PI generated by CART analysis.

than 2.0 mmol/L and peritonitis as independent predictors of pathologic PI. We also found, however, that hypotension or pressor use, acute kidney injury, the need for active mechanical ventilation, and absent bowel sounds were independent predictors of PI.

Our study has several important limitations that must be considered. The inherent limitations of retrospective design limit the granularity and reliability of the data available. Different practices at each of the participating centers, including the threshold for operation and the willingness to engage in discussions of withdrawal of care in the setting of PI, cannot adequately be measured between both individual providers and institutions. It is also important to note that our definition of pathologic PI, including both confirmed operative pathology and those patients who died owing to withdrawal of care, differs from that of many previous studies. Approximately 40% of patients in our study diagnosed with pathologic PI were in the withdrawal of care group. For future studies, the correlation of medical examiner data in this subset may improve the rate of definitive diagnosis. We must also highlight the potential impact of the absence of clear data on the slice of CT scanner used for each patient for detection of PI. While the improvement in CT technology has not been definitively shown to improve PI diagnosis, it is only logical that this would potentially be the case. For our present study, however, many of the centers upgraded CT technology over the study period. The precise timing of this upgrade with regard to what slice scanner was used could not be precisely defined for each individual patient in our retrospective design. Finally, the associated complications were pulled as data points from the hospital registry for this population. Differences in the method of diagnosis for specific entities (e.g., ventilator-associated pneumonia, urinary tract infection) may have existed both at individual centers and between centers in this retrospective study.

Despite these limitations, ours is the largest multicenter study of PI available in the present literature. Our findings demonstrate that the evaluation of PI remains a complex process that requires comprehensive evaluation of each individual patient to determine the appropriate course of treatment. Correlation with clinical history, examination, and laboratory evaluations are required but may be confounded by other clinical factors. Our study does demonstrate that hyperlactemia, in combination with either hypotension/pressor requirement or peritonitis, is strongly associated with the finding of pathologic PI in the majority of patients (Fig. 1). There is, however, a need for a prospective multicenter trial to expand our understanding of the optimal management of PI.

AUTHORSHIP

All authors have made contributions to the study design, data acquisition, and/or interpretation. Primary analysis was undertaken by J.J.D. and O.O. In addition, all authors contributed to drafting or revising the article and contributed to the final approval of the version submitted.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Gelman SF, Brandt LJ. Pneumatosis intestinalis and AIDS: a case report and review of the literature. *Am J Gastroenterol*. 1998;93:646–650.
2. Op de Beeck B, Peters K, Spinhoven MJ, Snoekckx A, Salgado R, Parizel PM. Asymptomatic pneumatosis intestinalis in AIDS. *JBR-BTR*. 2009;92: 253–255.
3. Zulke C, Ulbrich S, Graeb C, Hahn J, Strotzer M, Holler E, Jauch KW. Acute pneumatosis cystoides intestinalis following allogenic transplantation—the surgeon's dilemma. *Bone Marrow Transplant*. 2002;29:795–798.
4. Kwon HJ, Kim KW, Song GW, Kim DY, Chung SY, Hwang S, Lee SG. Pneumatosis intestinalis after liver transplantation. *Eur J Radiol*. 2011; 80:629–636.
5. Hepgur M, Ahluwalia MS, Anne M, Thomas J, Liu H, Schiff MD, Loud PA, Hahn TE, Bullard Dunn KM, McCarthy PL Jr. Medical management of pneumatosis intestinalis in patients undergoing allogenic blood and marrow transplantation. *Bone Marrow Transplant*. 2011;46:876–879.
6. Vijayakanthan N, Dhamanaskar K, Stewart L, Connolly J, Lebert 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;63:312–317.
7. 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;37:2194–2195.
8. Balbir-Gurman A, Brook OR, Chermesh I, Braun-Moscovici Y. Pneumatosis cystoides intestinalis in scleroderma-related conditions. *Intern Med J*. 2012;42:323–329.
9. Robertson MB, Choe KA, Joseph PM. Review of the abdominal manifestations of cystic fibrosis in the adult patient. *Radiographics*. 2006;26: 679–690.
10. Marinello DK, Rafael D, Paiva Edos S, Dominoni RL. Systemic lupus erythematosus complicated by intestinal vasculitis and pneumatosis intestinalis. *Rev Bras Reumatol*. 2010;50:596–602.
11. Shimojima Y, Ishii W, Matsuda M, Tojo K, Watanabe R, Ikeda S. Pneumatosis cystoides intestinalis in neuropsychiatric systemic lupus erythematosus with diabetes mellitus: a case report and literature review. *Mod Rheumatol*. 2011;21:415–419.
12. Nathan H, Singhal S, Cameron JL. Benign pneumatosis intestinalis in the setting of celiac disease. *J Gastrointest Surg*. 2006;10:890–894.
13. 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:CS139–CS142.
14. Kreiss C, Forohar F, Smithline AE, Brandt LJ. Pneumatosis intestinalis complicating *C. difficile* pseudomembranous colitis. *Am J Gastroenterol*. 1999;94:2560–2561.
15. Woo K, Major K, Kohanzadeh S, Allins AD. Laparotomy for visceral ischemia and gangrene. *Am Surg*. 2007;73:1006–1008.
16. Parker HH 3rd, Bynoe RP, Nottingham JM. Thrombosis of the portal venous system after splenectomy for trauma. *J Trauma*. 2003;54:193–196.
17. Tsai YM, Hsu KF, Yu JC, Chan DC, Liu YC. Life-threatening signs of ischemic bowel disease-portomesenteric venous gas. *J Trauma*. 2011; 71:E18.
18. Liao YT, Lin TH, Ko WJ. The early presence of pneumatosis in traumatic colonic perforation: a sequential computed tomography demonstration. *Am J Emerg Med*. 2010;28:645.
19. Shuck JM, Malan LJ, Hammar MD. Pneumatosis cystoides intestinalis due to blunt abdominal trauma. *J Trauma*. 1974;14:435–440.
20. Kelly BS Jr, Meyers P, Choe KA, Hurst J, Luchette FA. Traumatic pneumatosis cystoides intestinalis with portal venous air embolism. *J Trauma*. 1997;42:112–114.
21. Kingsley DD, Albrecht RM, Vogt DM. Gastric pneumatosis and hepatoportal venous gas in blunt trauma: clinical significance in a case report. *J Trauma*. 2000;49:961–963.
22. Rath T, Roeb E, Doppl WE. Pneumatosis coli as a rare complication of bowel preparation. *Endoscopy*. 2010;42(Suppl 2):E344–E345.
23. 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:W112–W117.

24. Ho LM, Paulson EK, Thompson WM. Pneumatosis intestinalis in the adult: benign to life-threatening causes. *AJR Am J Roentgenol*. 2007;188: 1604–1613.
25. Hou SK, Chern CH, How CK, Chen JD, Wang LM, Lee CH. Hepatic portal venous gas: clinical significance of computed tomography findings. *Am J Emerg Med*. 2004;22:214–218.
26. 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;26:601–603.
27. St Peter SD, Abbas MA, Kelly KA. The spectrum of pneumatosis intestinalis. *Arch Surg*. 2003;138:68–75.
28. 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;70:19–23, discussion 23–24.
29. 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:e582–e587.
30. Kirkpatrick ID, Kroeker MA, Greenberg HM. Biphasic CT with mesenteric angiography in the evaluation of acute mesenteric ischemia: initial experience. *Radiology*. 2003;229:91–98.
31. Smerud MJ, Johnson CD, Stephens DH. Diagnosis of bowel infarction: a comparison of plain films and CT scans in 23 cases. *AJR Am J Roentgenol*. 1990;154:99–103.
32. Peloponissios N, Halkic N, Pugnale M, Jornod P, Nordback P, Meyer A, Gillet M. Hepatic portal gas in adults: review of the literature and presentation of a consecutive series of 11 cases. *Arch Surg*. 2003;138: 136–170.
33. Naguib N, Mekhail P, Gupta V, Naguib N, Masoud A. Portal venous gas and pneumatosis intestinalis; radiologic signs and wide range of significance in surgery. *J Surg Educ*. 2012;69:47–51.
34. Khorram-Manesh A, Oden A. Management of hepatic portal venous gas and pneumatosis intestinalis in critically sick adult patients. *Scan J Gastroenterol*. 1009;44:1019–1020.
35. Wu JM, Liang JT. Pneumatosis intestinalis and hepatico-portal-mesenteric-splenic venous gas. *Dig Surg*. 2008;25:331–332.
36. Weisner W, Mortele K, 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 outome. *AJR Am J Roentgenol*. 2001;177:1319–1323.
37. 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;14:437–448.
38. 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: 506–510.

