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## The spectrum of pneumatosis intestinalis in the adult. A surgical dilemma

Giuseppe Tropeano, Marta Di Grezia, Caterina Puccioni, Valentina Bianchi, Gilda Pepe, Valeria Fico, Gaia Altieri, Giuseppe Brisinda

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### Abstract

Pneumatosis intestinalis (PI) is a striking radiological diagnosis. Formerly a rare diagnostic finding, it is becoming more frequently diagnosed due to the wider availability and improvement of computed tomography scan imaging. Once associated only with poor outcome, its clinical and prognostic significance nowadays has to be cross-referenced to the nature of the underlying condition. Multiple mechanisms of pathogenesis have been debated and multiple causes have been detected during the years. All this contributes to creating a broad range of clinical and radiological presentations. The management of patients presenting PI is related to the determining cause if it is identified. Otherwise, in particular if an association with portal venous gas and/or pneumoperitoneum is present, the eventual decision between surgery and non-operative management is challenging, even for stable patients, since this clinical condition is traditionally associated to intestinal ischemia and consequently to pending clinical collapse if not treated. Considering the wide variety of origin and outcomes, PI still remains for surgeons a demanding clinical entity. The manuscript is an updated narrative review and gives some suggestions that may help make the decisional process easier, identifying patients who can benefit from surgical intervention and those who can benefit from non-operative management avoiding unnecessary procedures.

**Key Words:** Pneumatosis intestinalis; Risk factors; Treatment; Portal venous gas; Portomesenteric pneumatosis

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**Core Tip:** Pneumatosis intestinalis (PI) represents a radiological diagnosis that must be understood correctly in order to follow the appropriate management. It is essential to identify the conditions that can evolve into transmural intestinal ischemia. It is also important to recognize those cases where PI can be managed conservatively. The integration of the clinical presentation, laboratory tests and abnormal abdominal physical examination can give indications on the path to follow. With this narrative review we have tried to provide a comprehensive analysis of the knowledge of this topic by proposing an algorithm to guide clinical decisions.

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## INTRODUCTION

Pneumatosis Intestinalis (PI) refers to a spectrum of diseases characterized by the presence of gas in the intestinal wall[1-4]. It was firstly described the 1700s by Du Vernoy, that detected gas in the bowel wall during a cadaver dissection.

The radiographic finding of PI can indicate a spectrum of underlying processes ranging from a benign finding to a life-threatening condition. It is possible to distinguish between “primary” and “secondary” PI[5-8]. Primary PI, also known as idiopathic or pneumocystis cystoides, is a pathologic condition characterized by the presence of gas-filled cysts in the sub-mucosa or sub-serosa especially of the colon[9-11]. Secondary PI is usually related to underlying pathological conditions (Table 1) and it is commonly characterized by the presence of linear or curvilinear gas balls in the intestinal wall[9,10,12-21]. Typically, the primary PI is asymptomatic and is not as frequent as the secondary PI (15% vs 85%)[1, 22].

Because of its rarity, PI is not yet completely clear from a pathophysiological, diagnostic and therapeutic point of view. Although radiographic PI is relatively common, there is no validated clinical tool to guide surgical management. This narrative review aims to summarize the existing evidence to better understand how to manage patients with this condition.

## MATERIAL AND METHOD

The review of the literature was conducted with the following method. A search was conducted on Pubmed for all articles published up to September 2022 with the following terms: “Pneumatosis intestinalis” OR “Portomesenteric pneumatosis” OR “intestinal pneumatosis”. A total of 206 articles were detected.

After evaluation of the full text, only 20 manuscripts were included for the draft of this review according to their pertinence in regards of the main topics. Inclusion criteria take in type of publication, study setting, reported outcome and date to publication.

Exclusion criteria were clinical case report, studies focused on specific groups. In particular, excluding case report, some of the 186 articles were excluded for being age specific (*i.e.*, pediatric patients), other for being focused on certain procedures or pathologies (*e.g.*, post-endoscopic procedures, pneumatosis cystoides) or, furthermore, for being of different area of interest (*e.g.*, articles focused just on imaging appearance).

The reference list of the articles evaluated in full text was screened for any other relevant article and those articles were evaluated according to the same criteria.

## PATHOGENESIS

The pathogenesis of PI is still unclear and probably is a combination of different theories considering how many diseases can be associated with pneumatosis[7,23,24].

Three are the main theories about the gas origin within the intestinal wall. There is the “mechanical theory” that speculates an intraluminal origin of gas: It seems to be a combination of an increased intraluminal pressure and an increased gut permeability[25]. It is possible that mucosal disruption due to inflammation or ischemia can predispose to an increase of intestinal wall permeability with the formation of small cysts in which the gas is trapped[26,27].

Table 1 Underlying pathological conditions

Pathological conditions	
Trauma[21,64-67]	Blunt/penetrating abdominal trauma
	Surgical anastomosis or bypass
Mechanical[68]	Pyloric obstruction or stenosis
	Duodenal obstruction or stenosis
	Bowel obstruction (volvulus, carcinoma, malrotation, intussusception)
Autoimmune[69-71]	Lupus enteritis
	Celiac sprue
	Polymyositis
	Dermatomyositis
	Polyarteritis nodosa
	Mixed connective tissue diseases
	Graft versus host disease
	Primary immunodeficiency
Malignancies[15]	Gastrointestinal cancer
	Leukemia
	Lymphoma
	Other malignancies
Inflammation[14,72]	Inflammatory bowel disease
	Appendicitis
	Diverticulitis
	Cholelithiasis
	Sarcoidosis
Vascular conditions[73]	Ischemia or infarction
	Diabetes
Pulmonary disease[74,75]	Chronic obstructive pulmonary disease
	Cystic fibrosis
	Asthma
Drugs[13,19,76-79]	Corticosteroids
	Chemotherapy and immunotherapy
	Immunosuppression
	Lactulose
	Trichloroethylene
	Sorbitol
	Alpha-glucosidase inhibitor
	Practolol
Diagnostic/therapeutic procedures[80,81]	Endoscopy
	Enema/colon idrotherapy
	Barium studies
Connective tissue disease/neurological[82,83]	Scleroderma
	Multiple sclerosis
	Hirschsprung disease

Other conditions[17,84]	Quadriplegia
	Amyloidosis
	Hemodialysis
	Pseudo-obstruction
	Whipple disease
	Cytomegalovirus infection
	COVID-19 infection

COVID-19: Corona virus infectious disease-2019.

The second theory hypothesizes that the source of the gas is the chest through the retroperitoneum from the alveolar rupture along vascular channels[25,28]. It is demonstrated for example in patients with asthma or bronchitis, in which alveolar air runs from the mediastinum descending to the mesenteric root and vessels[29].

The last theory is the “bacterial” one. It postulates that the gas produced from gas-producing bacteria can reach the intestinal wall if associated with mucosal injury. This theory was suggested from the evidence of the high hydrogen content of the cyst, that suggests a bacterial origin[30]. It seems that bacteria cause a higher hydrogen tension than the nitrogen tension in blood, causing an exit of hydrogen in the intraluminal compartment[25].

All these theories try to explain different aspects of a complex finding, related to several diseases and several clinical conditions from asymptomatic to fatal. It is probably due to this complexity that it is a challenge for the surgeon to predict the severity of PI and the need for surgery[31-34].

## CLINICAL AND LABORATORY ASSAY CORRELATION

Usually, PI was considered as a predictive sign of bowel ischemia, but with the improvement of the imaging techniques and its wider use, it was found also in asymptomatic patients[35,36]. For that reason, different studies tried to find a correlation between clinical findings, laboratory data and imaging, in order to distinguish between PI that needs surgery from PI that doesn't have any clinical significance[37,38].

### Clinical findings

Hemodynamic instability, hypotension, sepsis, abdominal rigidity or peritonism, adynamic ileus are associated with pathological PI. These signs and symptoms are directly related to transmural intestinal infarction (Figure 1); these patients need to be evaluated from a surgeon and often need a surgical exploration[39]. The surgical challenge is the patient that is hemodynamically stable, with or without abdominal pain but not peritonitis, in which it is more difficult to decide how to proceed[37].

The more common symptoms in patients with PI associated with bowel vascular impairment are abdominal pain, weight loss, constipation or diarrhea, less frequently bleeding or ileus[40]. Despite the clinical presentation, it seems that the severity of symptoms is not correlated with the severity of the amount of intramural gas at the computed tomography (CT) scan[41,42]. It is more reasonable to believe that the clinical manifestation of PI is related to the underlying diseases[25].

### Laboratory data

Several studies tried to identify some laboratory values that could help among the management strategies. Morris *et al*[10] found that pH values are higher in patients treated successfully conservatively than in patients that underwent to surgery as well as lactate are lower in the non-operative group than in the operative one. Moreover, Ferrada *et al*[39] found that lactate, creatinine, blood urea nitrogen (BUN), potassium and white blood cells (WBC) are higher in patients with pathologic PI (underlying bowel ischemia/infarction) than in benign PI (self-limiting cause which not requires surgical intervention). On the contrary, hemoglobin, hematocrit and bicarbonate are lower in patients with pathologic PI. Treyaud *et al*[43] analyzed many laboratory tests, finding that only WBC correlate significantly with an underlying bowel ischemia.



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**Figure 1** Intraoperative finding of diffuse ileal ischemia. (Personal observation).

Laboratory tests can also correlate with clinical outcome. Among these studies, Bani Hani *et al*[44] demonstrate that high lactate, low arterial CO<sub>2</sub>, low serum albumin and BUN are correlated with a worst outcome in patients with PI and in particular BUN is the most strongly associated. Also, Horowitz *et al*[45] tried to understand which laboratory test can predict the outcome of these patients. They found out that low bicarbonate levels (< 20 mmol/L), low pH (< 7.35) and lymphopenia (< 2.000/L) correlate with poor outcome. Although almost each laboratory test has been investigated in different studies, for some studies peritonitis and clinical exam remain the strongest predictors of outcome[39,44].

## RADIOLOGICAL DIAGNOSIS

PI can be considered as a manifestation of a pathologic condition. It is not possible to discriminate the presence of PI on the basis of physical examination nor by the presence of a particular symptom. Diagnosis is typically radiological, and it is based on finding linear or circular collections of gas in the bowel wall. CT scan is the gold standard for establishing the presence of PI along with, in some cases, the associated pathological conditions[46-48]. According to some studies, radiographic location seems also to have a clinical relevance since small bowel PI has a higher incidence of transmural ischemia than PI at colonic locations[39].

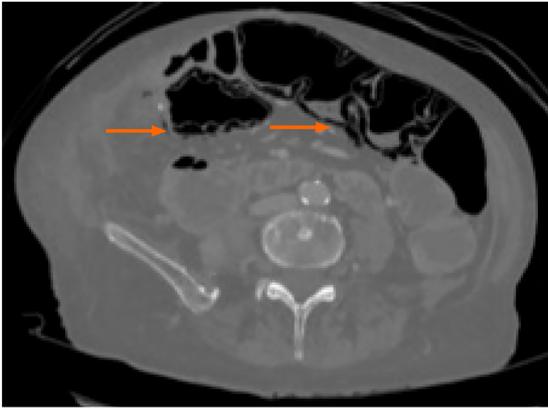
Moreover, according to some studies, also the radiological pattern of bubbles seems to be related to different underlying diseases. It is possible to recognize three different patterns: Cystoid or bubble-like pattern (Figure 2), in which gas looks like several cysts along the bowel wall and it is characteristic of the idiopathic PI; a linear pattern (Figure 3), in which gas has a curvilinear shape along the bowel and usually it is more associated with transmural infarction than the previous one; the circumferential pattern (Figure 4), in which gas appears circular along the bowel wall[49,50].

Conversely, Bani Hani *et al*[44] found that all the radiological distinctions between cystic or bubbly *vs* linear or curvilinear types of PI and the presence or absence of mesenteric stranding and thickening of bowel wall are not predictive of bowel ischemia. A recent machine learning model suggests that combined radiographic and clinical features can identify pathologic PI and aid in patient selection for surgery[37].

## MANAGEMENT

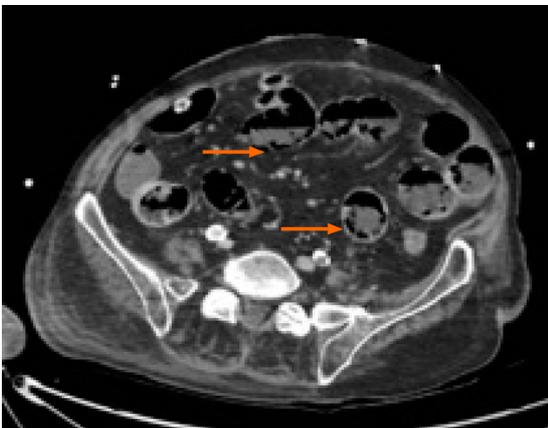
PI is not pathognomonic of bowel ischemia but should be a sign suspicious for alteration of the bowel vascularization. In this perspective, the treatment of PI should be guided by the underlying disease and the clinical conditions and not by the CT findings[51].

For what concerns the PI management, there should be a huge difference between symptomatic and asymptomatic patients. It is already known that PI is detectable in complete asymptomatic patients and CT scan alone cannot predict which patient will experience true intestinal ischemia[10]. Indeed, it is



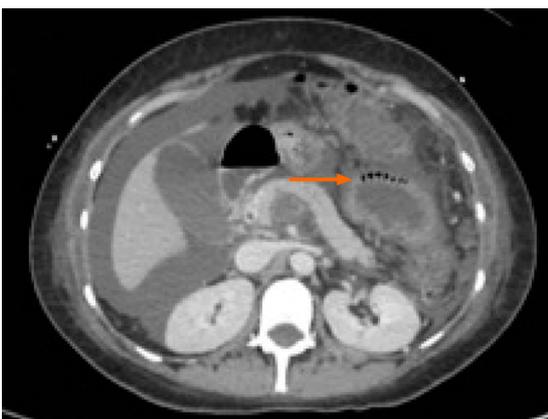
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**Figure 2** Computed tomography-scan with evidence of cystoid or bubble-like pattern pneumatosis intestinalis, identified by the orange arrow. (Personal observation).



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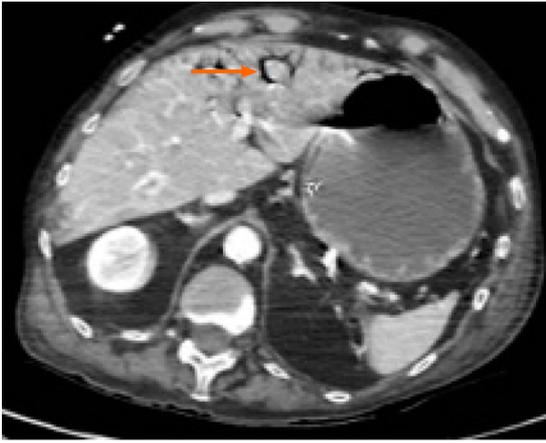
**Figure 3** Computed tomography-scan documenting a linear pattern at the level of the colonic wall, identified by the orange arrow. (Personal observation).



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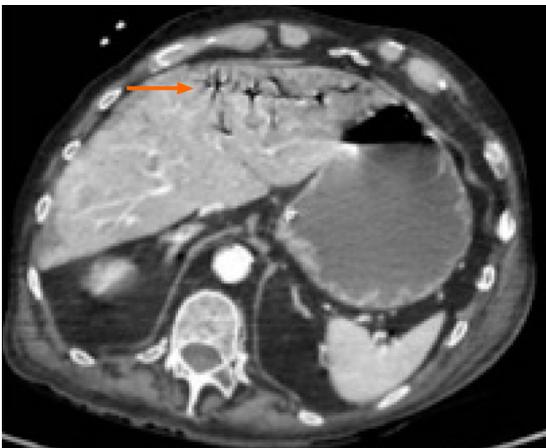
**Figure 4** Computed tomography-scan documenting circumferential pattern pneumatosis intestinalis, identified by the orange arrow. (Personal observation).

rare, but still possible, to find signs of PI in the CT scans of patients with mixed connective tissue diseases or bone marrow transplant, without any kind of clinical significance and in which conservative treatment with intestinal rest and antibiotics was successful[52,53]. Shinagare *et al*[54] reported a correlation between molecular targeted therapy (Bevacizumab, Sunitinib, Erlotinib, Cetuximab,



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Figure 5 Computed tomography-scan documenting localized portal venous gas, identified by the orange arrow. (Personal observation).



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Figure 6 Computed tomography-scan documenting diffuse portal venous gas, identified by the orange arrow. (Personal observation).

Sorafenib, Ipilimumab) and CT scan findings of PI with no clinical significance. Other clinical conditions associated with “benign” PI are bowel infections or inflammations, neoplastic bowel wall damage, ulceration, overdistension and previous gastrointestinal surgery[24,55-57].

Something that can help the surgeon in the decision-making process is the presence/absence of pneumatosis portalis. Pneumatosis portalis can be localized (Figure 5) or spread to multiple portal vessels (Figure 6). According to Knechtle *et al*[3], the presence of portomesenteric pneumatosis (PMP) is associated with a 37% of mortality. Usually, it is an ominous prognostic sign, due to a large amount of gas that migrate from the bowel wall to the veins, and it correlates with an advanced stage of PI and ischemia[50]. Although over the years the significance of PMP was questioned several times, there are many studies that underling the relation between PMP and outcome[58-60]. Wiesner *at al*[55] noticed that PMP was pathognomonic of transmural infarction in the 81% of patients and if PI and PMP were detected simultaneously in the same CT-scan, patient has the 91% of possibilities to have transmural bowel ischemia. Moreover, also Lassandro group[50] found a correlation between the PMP and the transmural ischemia, observing that the 91.5% of patients with PMP at the CT scan had also a proven bowel ischemia/infarction during surgery (Figure 7).

Summarizing, the management of peritonitic patients, with high lactate or low pH, and with PMP at the CT scan can be clear but it is still very hard to determine how to manage an asymptomatic patient with suspicious linear gas balls in the bowel wall. The results of the main clinical studies are shown in Table 2.

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## NEW PERSPECTIVES

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Considering the high complexity of this topic, we tried to formulate an algorithm in order to guide the

Table 2 Clinical studies in patients with pneumatosis intestinalis

Author	Type of study	Patients, n	Results
Ferrada <i>et al</i> [39]	Prospective Multicenter	One hundred twenty-seven patients with PI at CT scan	Mortality in the pathologic PI group <i>vs</i> benign PI group: 34% <i>vs</i> 13.9%. Patients with pathologic PI had hemodynamic instability, sepsis, peritonitis. The radiographic location is significant: Small bowel has a higher incidence of transmural ischemia than colon. Hepatic portal venous gas is suggestive for pathologic PI
Treyaud <i>et al</i> [43]	Retrospective Monocenter	One hundred eighty-seven patients with pi at CT scan	Location of PI nor the length of intestinal involvement correlate significantly with ischemia. The radiologic features that correlate with ischemia are PMP ( $P=0.009$ ) and the decreased mural contrast-enhancement ( $P < 0.001$ ). Among the laboratory tests, only WBC ( $> 12.000/mm^3$ ) correlates with bowel ischemia ( $P=0.03$ )
Morris <i>et al</i> [10]	Retrospective Monocenter	One hundred four patients with PI at CT scan	Mortality rate: 22%; 52% of patients were treated conservatively, with a mortality rate of 6%. Mortality rate of patients with PMP was 43%. No difference found in laboratory values between groups
Lassandro <i>et al</i> [49]	Retrospective Monocenter	One hundred two patients with PI at CT scan	Fifty-two percent of patients had surgical confirmation of bowel ischemia. 42.2% of patients had a bubblelike whereas in 59% it was linear. 75.5% of patients with linear pattern had bowel infarction. Mortality rate is 30.4%; it raises to 50% when PI is associated to PMP
Pickhardt <i>et al</i> [85]	Retrospective Monocenter	Five thousand three hundred sixty-eight Colonography scans, 0.11% with colonic PI	PI with curvilinear configuration. No clear if it was a pre-existing condition. No significant complications
Kernagis <i>et al</i> [48]	Retrospective Monocenter	Fifteen patients with PI at CT scan	Nine patients (60%) of symptomatic patients had transmural bowel infarction (4 small bowel, 5 colon)
Wiesner <i>et al</i> [55]	Retrospective Monocenter	Twenty-three patients with PI or PMP at CT scan and bowel ischemia	Twenty-two percent of patients showed partial mural bowel infarction, 78% of patients showed transmural bowel infarction. 70% of bubblelike PI was associated with bowel ischemia instead of the 88% of linear pattern. 81% of patients with PMP showed transmural infarction. Overall mortality 53%
Shinagare <i>et al</i> [54]	Retrospective Monocenter	Forty-eight patients with cancer and PI at CT scan	Thirty-nine patients were receiving molecular targeted therapy. Bevacizumab and Sunitinib were the most common drugs associated with PI. Median duration of molecular targeted therapy before PI or perforation was 3 mo. Asymptomatic patients 70.8%. Conservative PI treatment 100%
Huzar <i>et al</i> [9]	Retrospective Monocenter	One thousand one hundred twenty-nine patients admitted to Burn ICU	PI at CT scan 1.3%. Mortality rate of patients with PI was 73%. Explorative laparotomy in 2-3 h from the CT scan in 94% of the patients. PI involved both small bowel and colon 60%. Nonsurvivors had greater base deficit ( $P = 0.03$ ), open abdomen after surgery ( $P = 0.004$ )
Horowitz <i>et al</i> [45]	Retrospective Monocenter	Twenty-eight gynecological cancer patients and PI at CT scan	Patients symptomatic for abdominal pain 80%. Patients that did poorer were patients with preoperative acidosis, lower level of bicarbonate and lymphopenia

PI: Pneumatosis intestinalis; CT: Computed tomography; PMP: Portomesenteric pneumatosis; WBC: White blood cells; ICU: Intensive care unit.



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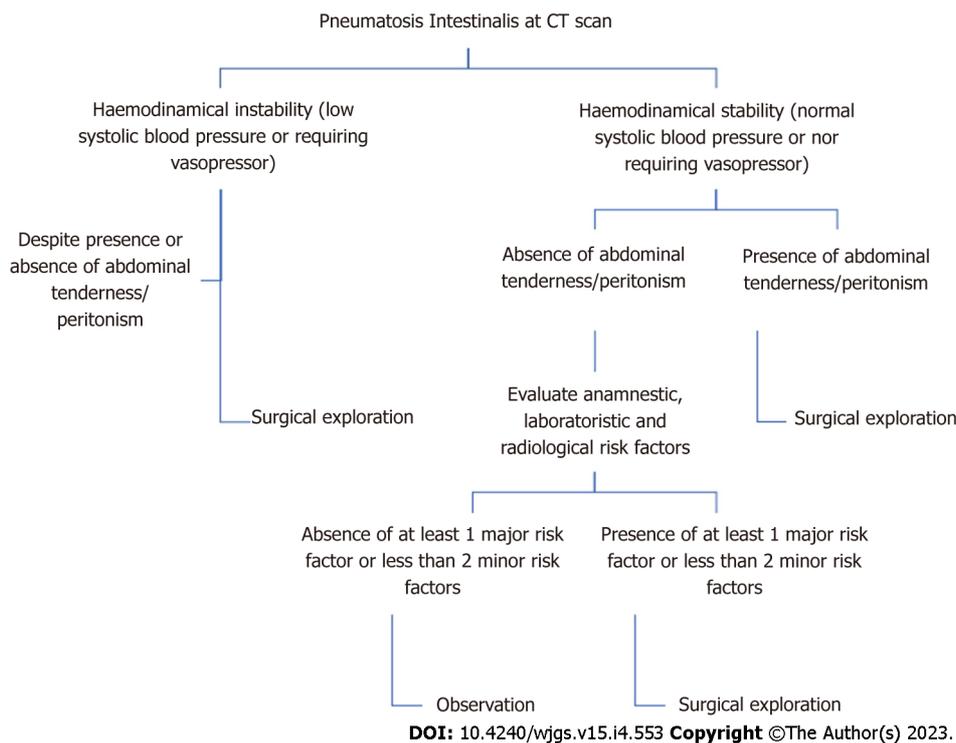
Figure 7 Intraoperative finding of transmural infarction with intestinal necrosis. (Personal observation).

surgeon in his decisional process (Figure 8). Analyzing data available in literature and data based on our experience, we selected some risk factors correlated with the presence of bowel ischemia at surgical exploration. We were able to identify some anamnestic, laboratory and radiological risk factors synthesized in Table 3.

**Table 3 Risk factors in patients with pneumatosis intestinalis**

Risk Factors	
Anamnestic	Vascular disease Atrial fibrillation
Major laboratory risk factors (blood sample)	Lac > 4 mmol/L LDH > 400 UI/L pH < 7.31 BUN > 50 mg/dL
Minor laboratory risk factor (blood sample)	WBC > 15.000/L Creatinine > 2 mg/dL HCO <sub>3</sub> <sup>-</sup> < 18 mmol/L Potassium 5.5 mmol/L
Radiological	Portomesenteric pneumatosis Pneumoperitoneum Free peritoneal fluid

LDH: Lactate Dehydrogenase; BUN: Blood urea nitrogen; WBC: White blood cells.



**Figure 8** Algorithm to guide clinical decisions in patients with pneumatosis intestinalis. CT: Computed tomography.

Laboratory parameters were then divided in major and minor risk factors. We wrote down a study protocol formulating an algorithm in order to help the surgeon decide if to undertake an operative or non-operative treatment. Patients are being enrolled treating them according to our algorithm (Figure 8).

In case of PI at the CT scan, distinction between hemodynamically stable or unstable patients is crucial. In case of instability surgical exploration is mandatory. In case of stability, clinical presentation plays a central role, considering as symptomatic the presence of abdominal tenderness or peritonism. If the patient is symptomatic, operative treatment is advocated. Otherwise, we rely on some anamnestic, laboratory and radiological parameters considered as risk factors (Table 3). We decided to surgically

treat asymptomatic patients if the following scenario is present. At least one anamnestic and radiological risk factor plus at least one major risk factor or two minor risk factors.

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## CONCLUSION

Taking into account all the possible causes and outcomes, PI represents a radiological finding which has to be correctly figured out in order to pursue the right management. It is crucial to identify the underlying condition in order to discriminate between patients who are at risk of transmural infarction from those with whom this condition could be managed without surgery[36,61]. Integration between clinical presentation, laboratory tests and abnormal abdominal physical examination can give hints about the pathway to follow. The aim is to promptly treat PI on vascular basis to avoid necrosis progression and to abstain from unnecessary and potentially harmful laparotomy/laparoscopy[32,62,63]. With this narrative review we tried to give a comprehensive analysis of the knowledge of this topic proposing an algorithm to guide clinical decisions. This manuscript has some limitations. Only one of the studies included was prospective (all the other were retrospective). The algorithm proposed, even if based on guidelines concerning various conditions in the setting of emergency care, should be validated by a prospective study.

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## FOOTNOTES

**Author contributions:** Tropeano G and Di Grezia M equally contributed to the drafting of the manuscript and must both be considered first author; Tropeano G, Di Grezia M, Puccioni C, Bianchi V and Brisinda G designed the research; Bianchi V, Pepe G, Fico V and Altieri G performed the research and selected the articles; Tropeano G, Di Grezia M and Puccioni C analyzed the data; Tropeano G, Di Grezia M, Puccioni C and Brisinda G reviewed the selected manuscripts and wrote the paper; All the authors read and approved the final manuscript.

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