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Acute Mesenteric Thrombosis: A Hematologist Perspective

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Acute vascular insufficiency of intestines (AVI) is a rare cause of severe abdominal pain contributing to 0.09% to 2% of admissions in surgical emergency. Despite its rarity, it needs early recognition because of its high mortality of 40% to 80% requiring timely diagnosis and prompt intervention. Occlusion of mesenteric vessels by arterial embolism (50%) or thrombosis (15% to 25%) and venous thrombosis (5%) are the predominant underlying causes. However, AVI may be nonocclusive in 20% to 30% of the patients.[1,2] Normally intestinal ischemia is prevented by its high perfusion through celiac mesenteric artery, superior mesenteric artery/inferior mesenteric artery, and a parallel system of venous drainage.[3] Therefore, bowel ischemia can occur only when blood supply is markedly reduced to 75% or more leading to a continuum of intestinal necrosis, perforation, infarction, or gangrene stimulating a severe inflammatory response that may be fatal.[4] Recently, activation of Janus kinase/transducer signaling pathway is proposed as an underlying mechanism for mesenteric ischemia.[5]

Bowel ischemia is of interest to the clinical hematologist because of its association with thromboembolism. Hematologists are frequently consulted for anticoagulating patients having AVI with or without concomitant bleeding risks. It is important for the hematologists to know the pathophysiology of bowel ischemia, rationale of anticoagulation, preferred anticoagulants, and the selection of patients for thrombophilia screening. This study was conducted to evaluate the clinicopathological spectrum and outcome of thrombosis in acute mesenteric ischemia at Aga Khan University, Karachi, Pakistan, for 5 years from January 2011 to October 2015 (ERC approval: 3872-Pat-ERC-15). *International Classification of Diseases (ICD)* classification 9 was used to identify admitted patients with AVI. Only patients with confirmed radiological or surgical diagnoses were included. Information was collected from medical chart and cross checked through computerized data system of the hospital. Demographics, risk factors, clinical features, laboratory/radiological investigations, duration of hospitalization, medical or surgical interventions, and mortality were studied. Complete blood count, coagulation profile, liver function test, and serum amylase, lipase, and lactate were analyzed. Thrombophilia screening and serum homocysteine were done at the doctor's discretion and therefore were analyzed where available. Data were collected, managed, edited, entered, and analyzed by SPSS version 22 and checked for normality. Median and interquartile range (IQR) for descriptive and Mann-Whitney for comparing groups were used for skewed data. Binary logistic regression was applied to determine the risk factors for mortality. Threshold of significance was a P value <.05.

ICD coding identified 117 patients for AVI. After removing duplication (n = 25) and patients with exclusive portal vein thrombosis (n = 3) or omental infarcts (n = 3), 86 individuals were evaluable for bowel ischemia. Mean age of the patients was 49.8 $\pm$ 18 years and male to female ratio was 1.6:1. Overall severe abdominal pain was the commonest presenting complain seen in 80% of patients. Other symptoms in the order of frequency were vomiting (41%), nausea (34%), constipation (23%), abdominal distention (21%), fever (19%), diarrhea (15%), and hematochezia (9%). Computed tomography scan was done in 80% of the patients for confirming diagnosis, and positive findings for bowel ischemia (pneumatosis intestinalis, gas in portal vein, or bowel dilation) were observed in only half of them. Superior mesenteric vein thrombosis (MVT) with concomitant involvement of portal vein, splenic vein, and inferior vena cava was observed in 26, 11, and 2 patients, respectively. Table 1 summarizes the demographics and main clinical findings in the patients with (n = 51) and without thrombosis (n = 35). Main causes identified were thrombosis of superior mesenteric vein (45%), nonocclusive mesenteric ischemia or NOMI (41%), and mesenteric artery occlusion

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Table 1. Summary of Clinical Details and Diagnostics in Patients With Acute Bowel Ischemia (n = 86).[a]

	Reference range	With thrombosis	Without thrombosis	*P*	All patients
n (%)	–	51 (59.3)	35 (40.7)	–	86 (100)
Gender M/F	–	37/14	17/18	–	54/32
Age in years, mean ± 1SD	–	49.2 ± 18.0	50.7 ± 18.1	.707	49.8 ± 18.0
Comorbidities, n (%)	–	17 (33.3)	17 (48.6)	.165	34 (39.5)
Abdominal pain, n (%)	–	43 (84.3)	26 (74.3)	.274	69 (80.2)
Fever, n (%)	–	9 (17.6)	7 (20)	.786	16 (18.6)
Hematochezia, n (%)	–	6 (11.8)	2 (5.7)	.320	8 (9.3)
Hemoglobin, g/dL	13.7-16.3 M 11.1-14.5 F	11.2 (12.2-9.4)	12.3 (13.5-10.3)	.702	11.3 (13.2-10.0)
Total white cell count, $\times 10^9$/L	4-10	13 (18.3-8.5)	9.8 (15.0-5.3)	.147	11.6 (17.2-11.6)
Platelet count, $\times 10^9$/L	150-400	233 (330-172)	172 (247-139)	.018[b]	208 (289-141)
Prothrombin time, seconds	9-11	12.5 (14.5-11.9)	12.6 (14.2-11.3)	.620	12.6 (14.3-11.8)
Total bilirubin, mg/dL	0.1-1.2	1.3 (2.7-0.5)	0.7 (1.6-0.4)	.363	1.0 (2.4-0.5)
Amylase, IU/L	28-100	46.5 (124.7-26)	77 (121-30)	.563	53 (121.5-27)
Lactate, mmol//L	0.5-2.2	2 (4.8-1.2)	4.7 (8.1-2.6)	.004[b]	3 (6.5-1.4)
Lipase, U/L	13-60	36 (140-27)	32.5 (115.5-24.2)	.565	34.5 (128-25.5)
CT scan done, n (%)	–	51 (100)	23 (65.7)		74 (80.0)
CT positive for AMI, n (%)	–	23 (45)	11 (31.4)	.202	34 (39.5)
Anticoagulation, n (%)	–	43 (84)	30 (85.7)	.861	66 (76.7)
Surgical intervention, n (%)	–	16 (31.4)	29 (82.9)	<.001[b]	45(52.3)
Surgical resection, n (%)	–	12 (23.5)	21 (60)	<.001[b]	33 (38.4)
Hospital stay, days	–	7 (14-3)	5 (12-2)	.395	6 (13-2)
Mortality, n (%)	–	13 (25.5)	17 (48.6)	.032[b]	30 (35)

Abbreviations: AMI, acute myocardial infarction; CT, computed tomography; F, female; IQR, interquartile range; M, male.
[a]Laboratory values are median (IQR 3-1).
[b]$P < .05$ is statistically significant; all continuous variables are median (IQR 3-1).

(14%). Sepsis was the most common underlying pathology in nonocclusive AVI (54%), while malignancy (n = 14 or 25%) and thrombophilia (n = 7 or 16%) were the predominant risk factors for MVT (Figure 1). Predisposing cancers include pancreatic (n = 6), hepatocellular carcinoma (n = 2), gastric (n = 1), colon (n = 1), Ewing's sarcoma (n = 1), polycythemia rubra vera (n = 1), and essential thrombocythemia (n = 1). Causes identified for mesenteric arterial occlusion (MAO) were atherosclerosis (n = 5) and atrial fibrillation (n = 3) (Figure 1). Anemia was a significant finding observed in 47% of females and 61% of males. Leukocytosis and thrombocytopenia were seen in 48 (56%) and 22 (26%) patients, respectively. Elevated serum amylase, lipase, and amylase were seen in 16%, 14%, and 41% of patients, respectively. Lower platelet counts and higher lactate levels were observed in patients with NOMI compared to patients with thrombotic disease ($P = .018$, .004, respectively). Only 12 and 17 patients were tested for serum homocysteine and thrombophilia screening. Hyperhomocysteinemia and thrombophilia were observed in 66% and 47% of tested patients. Overall, 85% patients were anticoagulated (30 with NOMI and 43 with MAO/MVT). Eight patients having thrombosis were not anticoagulated either due to immediate death (n = 4) or high risk of bleeding (n = 4). Surgical patients were anticoagulated with unfractionated heparin (n = 37) and later switched to either low-molecular-weight heparin (LMWH) (n = 13) or warfarin (n = 2). Surgery was performed in 45 (52%) of 86 patients and bowel resection was performed in 33 patients (75%). Surgical findings were significant for gangrenous bowel in 24% of patients, while perforations, infarction, ischemia, and necrosis were observed in another 29% of the patients. Nonsalvageable bowel was observed in 10% of patients with a 100% mortality. Surgical intervention ($P < .001$) with subsequent bowel resection ($P < .001$) was more frequent in NOMI than those without it (Table 1). Patients' stay in hospital ranged from 1 to 65 days with a median (IQR 3-1) of 6 days (13-2). Those who died had a shorter median hospital stay compared to the patients who were discharged alive (2.5 vs 7.5 days; $P = .001$). Overall, 35% of the patients died in hospital and the mortality was higher in patients with NOMI than those without it (49% vs 25%; $P = .032$). Regression analysis (Table 2) showed female gender, comorbidities, NOMI, abdominal pain, short hospital stay, prolonged prothrombin time (PT)/activated partial thromboplastin time, and high serum lactate as statistically significant predictors of mortality. However, only PT and serum lactate maintained this significance in multiple regression.

This study depicted few key differences with earlier reports such as a high prevalence of mesenteric venous thrombosis and in a relatively younger age-group. In contrast, earlier reports from West have showed MAO as the most important cause of bowel ischemia.[6] This was frequently reported in elderly population because of significant prevalence of cardiovascular morbidity in the aging population.[7] Our findings reconciled with the report from India where 48% of 117 patients with AVI had MVT at a median age of 53 years.[8]

The study showed no statistically significant differences in demographics and clinical presentations between the patients

Table 2. Multivariate Analysis for All-Cause Mortality in Patients Having Ischemic Bowel Disease (n = 86).

	Univariate logistics		Multiple regression	
Study parameters	Sig.	OR (95% CI; lower to upper)	Sig.	OR (95% CI; lower to upper)
Female gender	0.026	2.857 (1.136 to 7.186)	–	–
Coronary disease	0.025	6.75 (1.269 to 35.892)	–	–
Diabetes mellitus	0.036	3.709 (1.091 to 12.615)	–	–
Nonocclusive mesenteric ischemia	0.029	2.761 (1.106 to 6.888)	–	–
Chronic liver disease	0.010	16.739 (1.948 to 143.857)	–	–
Abdominal pain	0.001	11.657 (3.635 to 37.386)	–	–
Hospital stay	0.009	1.11 (1.026 to 1.2)	–	–
Prothrombin time	0.033	0.848 (0.729 to 0.987)	0.007	1.146 (1.037 to 1.267)
Activated partial thromboplastin time	0.030	0.947 (0.902 to 0.995)	–	–
Serum lactate levels	0.004	0.759 (0.627 to 0.918)	0.016	0.762 (0.61 to 0.95)

Abbreviations: OR, odd ratio; Sig, significance level.

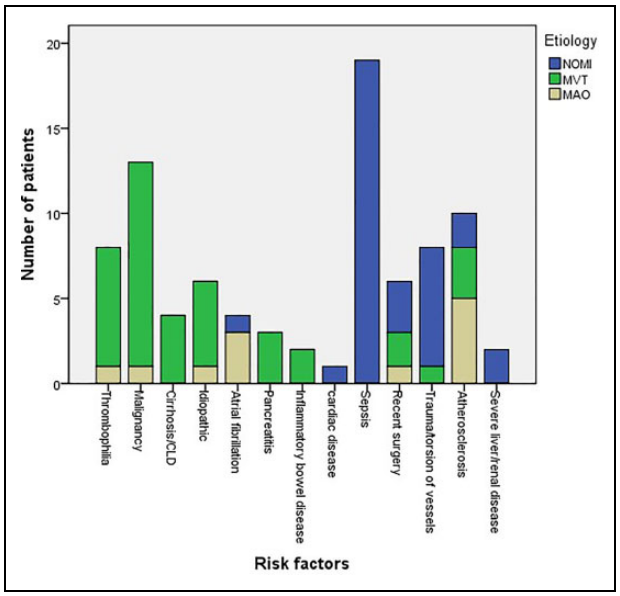

Figure 1. Risk factors for bowel ischemia in 86 patients according to underlying etiology: nonocclusive mesenteric ischemia (NOMI), mesenteric vein thrombosis (MVT), and mesenteric arterial occlusion (MAO).

with or without thrombosis. Patients with thrombotic disease presented with higher platelet count ($P = .018$), lower lactate ($P = .004$), required less surgical intervention and bowel resection ($P < 0.001$), and had a lower morality ($P = .032$) when compared to nonthrombotic patients. Malignancy and thrombophilia were the predominant underlying pathology for MVT as reported earlier,[9] and 50% of these patients having thrombophilia had previous history of recurrent spontaneous venous thromboembolism (VTE). Management of MVT is challenging. It requires multidisciplinary approach involving hematologists having special interest in thrombosis. The principles and practices of treating other VTE are applicable to some extent to MVT as well. Hematologists are frequently consulted for thrombophilia screening. Available evidence does not favor such screening in unselected patients. In this study, only 20% of the patients were screened for inherited thrombophilia based on the institutional criteria of screening young patients (<40 years of age) with no other identifiable cause. Moreover, British Committee of Standards in Hematology guidelines do not recommend thrombophilia testing after initial episode of intra-abdominal thrombosis because of its indeterminate value in defining thrombotic recurrence and the duration of anticoagulation.[10] However, testing for JAK 2 mutation may be considered in the diagnosis of unprovoked mesenteric thrombosis.[11]

Systemic anticoagulation is recommended in all patients with AVI to prevent thrombus development or propagation, vessel blockage, and bowel infarction provided there is a low risk of hemorrhage. Moreover, anticoagulation is typically continued following surgical exploration to avoid new thrombus formation.[1] Success rate of anticoagulation is reported high at 95% in venous mesenteric ischemia with a lower recurrence rate and mortality (13%) in heparinized patients.[12] Stable and symptom-free patients may be switched to warfarin for 3 to 6 months if risk factors are reversible. In contrast, anticoagulation should be continued indefinitely for unknown or persistent risk factors.[13] It is also suggested to anticoagulate an incidental MVT particularly if the patient has un underlying thrombophilia or previous history of VTE,[14] and the duration of anticoagulation may be similar to symptomatic MVT.[13] During this study, 85% of patients with AVI were heparinized initially and continued with either LMWH or vitamin K agonist. None of the patients received direct oral anticoagulants (DOACs). Direct oral anticoagulants are an attractive option for treating bowel ischemia because of fixed dosing, no laboratory monitoring, and absent drug, disease, and food interactions. Few have reported successful treatment with DOACs in non-neoplastic portal vein thrombosis,[15,16] but more evidence is needed prior to their usage because of significant gastrointestinal bleeding risk (with at least some of the DOACs).

This study showed that patients with mesenteric thrombosis had better prognosis than nonthrombotic bowel ischemia. Prompt anticoagulation and surgical intervention (as per need) were instrumental in successful management.

Authors' Note

Data can be provided by corresponding author on request. The study was designed and supervised by B.M. Data were collected by Z.M. and analyzed by B.M. Manuscript was written by B.M., Z.M., and Z.F.S. Initial draft was critically reviewed and approved by H.Z.

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