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Association of endotoxaemia & gut permeability with complications of acute pancreatitis: Secondary analysis of data

Namrata Singh[1], Ujjwal Sonika[1], Praneeth Moka[1], Brij Sharma[1], Vikas Sachdev[1], Sushil Kumar Mishra[1], Ashish Datt Upadhyay[2] & Anoop Saraya[1]

Departments of [1]Gastroenterology & [2]Biostatistics, All India Institute of Medical Sciences, New Delhi, India

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***Background & objectives*: In acute pancreatitis (AP) gut barrier dysfunction is considered as an important predisposing factor leading to increased intestinal permeability (IP). In this study a pooled analysis of data published in our previous four studies on various aspects of gut permeability and endotoxaemia in patients with AP was attempted to find an association between increased IP and severity of disease and associated complications.**

***Methods*: This study was a pooled analysis of data of four previously published prospective studies on AP. Gut permeability, assessed by lactulose/mannitol excretion in urine and endotoxin core antibodies type IgG and IgM (EndoCab IgG and IgM) were measured on days zero and seven (D0 and D7) of admission. All patients received standard treatment of AP. We studied whether IgG and IgM anti-endotoxin titres and lactulose-mannitol ratio (LMR) at admission and D7 were associated with organ failure, infection and mortality.**

***Results*: The titres of anti-endotoxin IgG and IgM were lower in all patients of AP (n=204), both in mild AP (n=24) and severe AP (n=180) in the first week, compared to controls (n=15). There was no significant difference in serum IgG and IgM anti-endotoxin levels and LMR at baseline and at D7 among patients with organ failure, infection and mortality.**

***Interpretation & conclusions*: Our findings showed that serum IgG and IgM anti-endotoxin titres and LMR at admission and at day 7 were not associated with organ failure, infection, and death of patients with AP.**

Key words Acute pancreatitis - endotoxaemia - intestinal permeability - mortality - organ failure

In acute pancreatitis (AP), mortality during late phase occurs due to the development of severe pancreatic and peripancreatic infection leading to sepsis and multiorgan dysfunction. An important predisposing factor for infection is gut barrier dysfunction. Both experimental and human studies have demonstrated increased intestinal permeability (IP) in severe AP[1-6]. AP-induced hypovolaemia due to endothelial barrier leakage and gut arteriovenous shunting causes intestinal ischaemia and reperfusion injury with concomitant gut barrier dysfunction[7]. Increase in IP results in translocation of Gram-negative bacteria (GNB)

through the lymphatics via the mesenteric nodes[8,9]. An antibody response is stimulated against GNB endotoxins attached to the cell wall. Some studies have noted that endotoxaemia is associated with systemic inflammatory response syndrome (SIRS), multiorgan failure and high mortality[10,11].

In our previous study on the role of probiotics on gut permeability and endotoxaemia in patients of AP, no significant trend was identified for an effect of probiotics on gut permeability or endotoxaemia in AP[12]. However, this study was underpowered owing to premature study termination. In another study to determine the non-inferiority of early enteral feeding through nasogastric (NG) compared to nasojejunal (NJ) route on infectious complications in patients with severe AP, infectious complications were found to be within the non-inferiority limit[13]. Pain in refeeding, IP and endotoxaemia were comparable in both groups. We published four studies[12-15] on AP during 2011 to 2014 which looked into IP and endotoxaemia in patients with AP. In the present study, a pooled analysis of data published in these four studies[12-15] was attempted with the hypothesis that the increased IP leads to severe disease in patients with AP along with increased complications and mortality.

Material & Methods

This study was a secondary pooled data analysis of our four previously conducted prospective studies[12-15] between June 2006 and December 2011. Patients of AP admitted in the department of Gastroenterology and Human Nutrition Unit of the All India Institute of Medical Sciences (AIIMS), New Delhi, India, during these studies were included for data analysis. Patients who presented with proven or suspected infected pancreatic necrosis and patients who had been put on enteral nutrition before admission were excluded from the analysis.

AP was diagnosed in the presence of at least two of the following: (*i*) Presence of pancreatic pain; (*ii*) at least three-fold rise in serum amylase; and (*iii*) evidence of AP on imaging studies.

The amount of pancreatic necrosis was graded as <30, 30-50 and >50 per cent. Computed tomography severity index (CTSI) was calculated as per criteria laid down by Balthazar *et al*[16]. Severe AP (SAP) was defined by the presence of at least one of the following criteria: (*i*) failure of one or more organ as defined by the Atlanta classification; (*ii*) an Acute Physiology and Chronic Health Evaluation II score >8; and/or (*iii*) CTSI >7[17]. Patients with functional dyspepsia who attended the outpatient clinic were included as controls to estimate the normal values of anti-endotoxins and lactulose-mannitol ratio (LMR).

Management of acute pancreatitis patients: All patients were treated either in the gastroenterology ward or intensive care unit. Enteral feeding was started early and calorie intake was increased gradually from 500 to 2000 kcal/day and then continued until the patient resumed a near-normal diet. The enteral feed was prepared in the hospital kitchen and its tolerability was monitored by the treating physicians. Antibiotics were started, if (*i*) fever >38°C for >48 h, (*ii*) total leucocyte count >16,000/cumm, (*iii*) evidence of any extra-pancreatic infection, (*iv*) evidence of gas in pancreatic bed on CT scan, (*v*) in the second week of illness if patient continued to have features of SIRS, or (*vi*) when any organism was grown in culture of blood or any of the body fluids. Percutaneous drainage of collections was done in the presence of persistent SIRS or organ failure despite the use of antibiotics for at least 48 h. In patients with organ failure, organ support systems were used, as needed. Blood cultures were done at least twice a week in all patients with suspected sepsis. Drain fluid/pus was sent for cultures every alternate day. Endotracheal aspirate/sputum was sent for cultures for patients with suspected pneumonia.

Measurement of intestinal permeability: IP (LMR) was measured by urinary LM test, in the enrolled patients on day zero (D0) of their admission with a repeat assessment done on D7. Patients received 50 ml of water containing 10 g lactulose and 5 g mannitol either orally or through a nasogastric tube. Urine was collected for five hours in a receptacle with 0.2 ml of 2 per cent chlorhexidine to avoid bacterial overgrowth. The total urinary volume was measured, and two aliquots of urine (10 ml each) were immediately frozen to −70°C until analysis. Lactulose was estimated using Seliwanoff's method[18]. Mannitol was estimated using the Corcoran and Page method[19]. The ratio of above lactulose and mannitol values was thus computed and defined as the LMR.

Measurement of endotoxaemia: Endotoxaemia, as measured by anti-endotoxin IgG and IgM, was measured with the EndoCab ELISA kit (Hycult Biotechnology, The Netherlands). The assay is based on a solid-phase sandwich ELISA and detects

and quantifies antibodies against endotoxin. The methodology used for measurement of IP and endotoxaemia was similar in all the four studies pooled for this analysis.

Statistical analysis: Data were analyzed by Statistic Software Stata 11.1 (StataCorp, Texas, USA), and presented in mean ± standard deviation/median (minimum-maximum) and frequency (%). Categorical variables were compared among groups by Chi-square/Fisher's exact test. Continuous variables following normal distribution were compared among the groups by independent *t* test/one-way Anova followed by *post hoc* comparison using Bonferroni correction. Skewed continuous variables were compared among the groups by Wilcoxon rank-sum/Kruskal-Wallis test followed by multiple comparisons using Dunn's test with Bonferroni correction.

Results

A total of 204 patients of AP who had undergone either serum anti-endotoxin antibody testing or LMR were included, of whom 180 had severe disease. Males constituted eight (33.3%) patients of mild AP, 88 (63.3%) of SAP in the first week and 25 (61%) patients of SAP presenting beyond the first week of illness ($P<0.05$). Baseline characteristics of all the patients are shown in Table I.

Anti-endotoxin antibodies and lactulose-mannitol ratio: Table II shows anti-endotoxin IgG and IgM levels

Table I. Baseline characteristics of patients with acute pancreatitis (AP)

Variable(s)	Group 1 Mild (n=24)	Group 2 Severe ≤ 7 days between pain and admission (n=139)	Group 3 Severe > 7 days between pain and admission (n=41)
Age (yr)	43.1±19.4	38.6±15.5	40±14.7
Males, n (%)	8 (33.33)	88 (63.31)*	25 (60.98)*
Aetiology, n (%)			
Alcohol	2 (8.4)	45 (32.4)***	24 (58.6)†††,***
Biliary	10 (41.7)	49 (35.3)	5 (12.2)
Post-ERCP	7 (29.2)	8 (5.8)	0 (0)
Idiopathic	5 (20.8)	37 (26.6)	12 (29.3)
Organ failure, n (%)			
Response failure	-	78 (56.2)***	26 (63.4)***
Renal failure	-	36 (25.9)***	15 (36.6)***
GI bleed	-	4 (2.9)	1 (2.4)
APACHE II	2 (1-4)	7 (0-24)***	8 (3-19)***
CTSI	0 (0-0)	6 (0-10)***	6 (1-10)***
Hb (g/dl)	10.9 (6.9-16.2)	11.6 (7.3-19.9)	11.3 (7.3-17)
Urea (mg/dl)	30 (16-72)	1 (0.1-9.2)	1.1 (0.4-9.7)
Creatinine (mg/dl)	1 (0.6-10)	1 (0.1-9.2)	1.1 (0.4-9.7)
AST (IU)	44 (29-409)	50.5 (18-1498)	56.5 (14-432)
ALT (IU)	62 (32-339)	45 (11-939)	46 (11-386)
SAP (IU)	350 (147-961)	210 (54-935)*	176 (66-934)*
Total protein (g/dl)	6.9 (5.6-9.2)	6.3 (3-8.7)	6.8 (5.4-8.2)
Albumin (g/dl)	3.8 (3.4-5.7)	3.1 (1.4-5.1)***	3.2 (2.1-4.4)***
ICU stay (days)	0 (0-3)	0 (0-40)	0 (0-27)
Hospital stay (days)	5 (2-10)	12 (1-86)***	18 (1-101)***,†††

*$P<0.05$, ***<0.001 compared to group 1; ††† <0.001 compared to group 2. Values are expressed as median (minimum-maximum). ERCP, endoscopic retrograde cholangiopancreatography; APACHE, acute physiology and chronic health evaluation; CTSI, computed tomography severity index; Hb, haemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAP, serum alkaline phosphatase; ICU, intensive care unit; GI, gastrointestinal

and LMR on the day of admission and D7 in patients with mild and severe AP. IgM and IgG anti-endotoxin antibodies were lower in all patients of AP compared to controls but were significantly lower in patients with mild AP and SAP within the first week of illness compared to patients with SAP presenting beyond the first week of illness. LMR was not higher in patients of SAP compared to patients of mild AP and controls.

Anti-endotoxin antibodies and LMR with organ failure: Table III shows the levels of anti-endotoxin antibodies IgG and IgM and LMR at D0 and D7 in patients of severe AP. There was no significant difference in levels of anti-endotoxin IgG and IgM among patients with organ failure compared to those without organ failure at D0 and D7. Rising trend of IgG anti-endotoxin antibodies was found in 50/74 (67.5%) patients with organ failure and in 26/55 (47.3%) patients without organ failure (P<0.05).

In SAP patients (n=180), at baseline, the median IgG anti-endotoxin titre was 140 (4-1600) GMU/ml among patients with organ failure (n=110) and 180 (4-1760) GMU/ml among patients without organ failure (n=70), while at D7, the median IgG anti-endotoxin antibody titre was 140 (18-1600) GMU/ml in patients with organ failure compared to 174 (2-1640) GMU/ml among

Table II. Markers of endotoxaemia and intestinal permeability in patients with acute pancreatitis (AP)

Biochemical outcomes	Controls (n=15)	Group 1 Mild AP (n=24)		Group 2 Severe AP ≤ seven days between pain and admission (n=139)		Group 3 Severe AP > seven days between pain and admission (n=41)	
		n		n		n	
IgG (GMU/ml)	520 (194, 960)	17	120 (20, 290)	117	140 (4, 1760)	33	290 (14, 1600)*,†
Change from day 0 to day 7		14	90 (−560, 820)	100	−4 (−700, 1540)**	29	−12 (−1540, 1520)**
Increment from day 0 to day 7			3 (21.4)		58 (58)*		18 (62.1)*
IgM (MMU/ml)	92.6 (60.6, 168)	17	61 (13, 230)	122	47 (2, 180)	33	71.4 (2, 147)†
Change from day 0 to day 7		14	10.5 (−36, 86)	99	−1 (−765, 144)	25	3.9 (−118, 120)
Increment from day 0 to day 7			6 (42.9)		53 (53.5)		10 (40)
Lactulose-mannitol ratio	0.128 (0.02, 0.66)	11	0.25 (0.4, 1.85)	111	0.14 (0.01, 30)	25	0.09 (0.02, 0.56)**,††
Change from day 0 to day 7		11	0.05 (−0.67, 1.27)	83	0.01 (−4.9, 2.98)	16	−0.012 (0.07, 0.34)
Reduction from day 0 to day 7			8 (72.73)		47 (56.63)		6 (37.50)

Values are expressed as median (minimum-maximum), frequency (%). Change from day 0 to 7: - suggests increment. P^{*}<0.5, **<0.01 compared to group 1; †<0.05, ††<0.01 compared to group 2. GMU, IgG median-unit; MMU, IgM median-unit

Table III. Markers of endotoxaemia and intestinal permeability in patients with severe acute pancreatitis with organ failure (n=180)

Variables	Any organ failure (n=110)		No organ failure (n=70)	
	n		n	
IgG0, GMU/ml	89	140 (4-1600)	61	180 (4-1760)
IgG7, GMU/ml	75	140 (18-1600)	55	174 (2-1640)
IgM0, MMU/ml	94	52 (2-178)	61	44 (4-180)
IgM7, MMU/ml	80	55 (7-801)	53	50 (8-350)
LMR0	86	0.1178 (0.012-3)	50	0.1535 (0.008-1.29)
LMR7	59	0.124 (0.009-5)	40	0.1565 (0.009-1.25)

Values are expressed as median (minimum-maximum). LMR, lactulose-mannitol ratio; Suffix 0, test done at day 0 of admission; Suffix 7, test done at day 7 of admission. GMU, IgG median-unit; MMU, IgM median-unit

Table IV. Markers of endotoxaemia and intestinal permeability in patients with severe acute pancreatitis in relation to infection (n=180)

Variables	Any infection (n=44)		No infection (n=136)	
	n		n	
IgG0, GMU/ml	37	168 (4-840)	113	160 (4-1760)
IgG7, GMU/ml	31	214 (20-1160)	99	160 (2-1640)
IgM0, MMU/ml	38	49 (2-162)	117	50 (2-180)
IgM7, MMU/ml	37	57 (20-350)	96	50 (7-801)
LMR0	31	0.117 (0.0125-3)	105	0.132 (0.008-3)
LMR7	21	0.124 (0.015-5)	78	0.149 (0.009-2.6)

Values are expressed as median (minimum-maximum). LMR, lactulose-mannitol ratio; Suffix 0, test done at day 0 of admission; Suffix 7, test done at day 7 of admission. GMU, IgG median-unit; MMU, IgM median-unit

Table V. Markers of endotoxaemia and intestinal permeability in patients with severe acute pancreatitis in relation to mortality (n=180)

Variables	Survivors (n=149)		Non-survivors (n=31)	
	n		n	
IgG0, GMU/ml	126	160 (4-1760)	24	200 (28-1600)
IgG7, GMU/ml	113	160 (2-1640)	17	262 (32-1600)
IgM0, MMU/ml	129	50 (2-180)	26	56 (2-160)
IgM7, MMU/ml	115	55 (7-801)	18	60 (20-106)
LMR0	112	0.143 (0.008-3)	24	0.106 (0.020-3)
LMR7	86	0.149 (0.009-5)	13	0.133 (0.015-1.9)

Values are expressed as median (minimum-maximum). LMR, lactulose-mannitol ratio; Suffix 0, test done at day 0 of admission; Suffix 7, test done at day 7 of admission. GMU, IgG median-unit; MMU, IgM median-unit

patients without organ failure ($P<0.05$). There was no difference in LMR at D0 and D7 between patients who developed organ failure and those who did not.

Anti-endotoxin antibody titres and LMR with infection: Table IV shows anti-endotoxin antibody titres and LMR among patients of SAP who developed an infection. There was no significant difference in anti-endotoxin IgG and IgM and LMR among patients who developed infection subsequently compared to those who did not develop an infection.

Anti-endotoxin antibody titres and LMR with mortality: Table V shows the association of anti-endotoxin antibody titres and LMR with mortality among patients with SAP. There was no significant difference in anti-endotoxin antibody titres and LMR in non-survivors compared to survivors.

The proportion of patients with alcohol as aetiology was similar between various groups (infection vs. no infection; mortality vs. no mortality; organ failure vs. no organ failure).

Discussion

In this secondary pooled data analysis, a total of 204 patients with AP were included. Endotoxin, which is a constituent of GNB cell wall, is implicated to be involved in the development of systemic inflammatory response syndrome (SIRS) and severe sepsis[20]. Endotoxaemia has been shown to be directly related to the severity of episodes of AP[21,22]. It is transient and may not be detected by intermittent blood sampling[23].

As shown in previous studies[21,24] no significant difference in anti-endotoxin IgM levels was observed between mild AP and SAP at admission. IgG anti-endotoxin antibodies, although not significantly different between mild AP and SAP at admission, were increased by a greater value and in a greater number of patients of SAP compared to mild AP over seven days. However, in patients with SAP presenting beyond the first week of illness, the median IgG and IgM anti-endotoxin antibodies were lower than controls but higher than patients of mild AP and SAP presenting within the first week of illness. Windsor *et al*[23] reported no correlation between the changes in IgM anti-endotoxin

antibody concentration over days and clinical outcome in patients of AP. Unlike some previous studies[21,24] but similar to Windsor *et al*[23], no significant difference in change in IgM levels was found between mild AP and SAP. Unlike Windsor *et al*[23], who checked serum IgG anti-endotoxin antibody levels for seven days from admission and reported that falling IgG titres predicted multiple organ failure, we found that rising IgG anti-endotoxin antibodies were associated more often with organ failure in patients with severe AP.

However, in a subset of patients of SAP who presented within the first week of illness, the median serum IgG anti-endotoxin antibody titre was lower at baseline and remained relatively lower than in patients without organ failure. A greater number of patients of SAP succumbed to organ failure within seven days of admission among patients with the lowest IgG anti-endotoxin levels so that their D7 anti-endotoxin titres were not available for analysis. This led to the paradoxically significant value of higher median serum IgG levels in patients without organ failure at D7. It is possible that serum IgG anti-endotoxin antibody has fallen to its nadir by the time of admission (1 to 2 wk) and that it may be rising subsequently, earlier in patients without organ failure and later and slowly in patients with organ failure who did not succumb to their organ failure. The absolute value of serum IgG anti-endotoxin antibody titre at a single point of time was not significantly different among patients with organ failure compared to patients without organ failure.

Ammori *et al*[22] also reported that systemic endotoxin exposure in the early phase of AP was not associated with systemic bacterial translocation. Serum IgG and IgM anti-endotoxin titres and their changes over time were not associated with subsequent risk of infection in our study. Unlike Bose *et al*[25] who reported that serum IgG and IgM anti-endotoxin titres were lower in patients with major complications, including infection, our analysis did not show an association of serum anti-endotoxin antibody titres with subsequent risk of infection. It is possible that endotoxaemia in the early phase is related to early organ failure but not associated with the risk of infection in the later phase.

Unlike some previous studies[14,25] which reported that serum IgG and IgM anti-endotoxin antibody titres were lower in non-survivors than in survivors, no such association was observed in the present study. IgG anti-endotoxin antibodies were lowest in mild AP and decreased further in these patients at D7. These were higher in patients with SAP and were increasing at D7 with the rising trend more often observed in patients with organ failure. There are various possible reasons for this finding. Patients with mild AP were more often admitted within one day of illness when the antibody titre might be very low. Patients with SAP were more often admitted on the fourth to fifth day of illness by which time, the trend of Ig to increase might have begun. Endotoxaemia may be only either an epiphenomenon or an aggravating factor, related to organ failure caused by a cytokine storm in the early phase, and may not be linked directly to mortality. It is also possible that the reasons for the reduction in serum IgG and IgM anti-endotoxin antibodies may not be due to binding to circulating endotoxin and subsequent removal[23] alone but may be related to binding of antibodies to endogenous antigens, molecularly mimicking the GNB endotoxin[23]. The subsequent increase in serum Ig against endotoxin may indicate recovery of immunity. A similar phenomenon of increasing anti-endotoxin antibodies as a marker of recovery has been proposed by Maury *et al*[20] in patients with severe sepsis. This similarity is expected because of the striking similarities in cytokines and inflammatory mediator profiles in patients with SAP and sepsis[26].

It is reported that IP has been found to increase within the first 72 h and it correlates strongly with the clinical outcome of the patient[27,28]. Juvonen *et al*[29] have suggested that after an initial increase, the IP in a patient gets restored between D8 and D45 of the illness. We found that IP, both in mild AP and SAP presenting either within or beyond the first week of illness, was similar to controls[14], which was in contrast to the previous findings[28]. This could be related to later referrals to our hospital. Although our controls[14] had higher LMR than widely reported values, they were apparently healthy people without any factor predisposing to increased gut permeability.

LMR was not significantly different among patients with organ failure, infection and mortality compared to those without these complications. A meta-analysis of 18 studies reported that gut barrier dysfunction was present in three out of five patients with AP and that the prevalence was not affected by severity[30]. More studies are warranted to assess gut permeability, using different probes in AP.

The strength of our study was the large number of patients with severe AP and the estimation of study parameters using validated methods. However, the retrospective data analysis can lead to bias and is the major limitation of this study.

In summary, the present pooled data analysis showed that serum IgG and IgM anti-endotoxin antibodies and LMR on admission day and at day 7 were not associated with the risk of infection, organ failure and mortality in patients with AP.

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For correspondence: Dr Anoop Saraya, Department of Gastroenterology & Human Nutrition Unit, Teaching Block, All India Institute of Medical Sciences, New Delhi 110 029, India
e-mail: ansaraya@yahoo.com