Systematic review

Meta-analysis of gut barrier dysfunction in patients with acute pancreatitis

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Background: **The gut is implicated in the pathogenesis of acute pancreatitis but there is discrepancy between individual studies regarding the prevalence of gut barrier dysfunction in patients with acute pancreatitis. The aim of this study was to determine the prevalence of gut barrier dysfunction in acute pancreatitis, the effect of different co-variables, and changes in gut barrier function associated with the use of various therapeutic modalities.**

Methods: **A literature search was performed using PRISMA and MOOSE guidelines. Summary estimates were presented as pooled prevalence of gut barrier dysfunction and the associated 95 per cent c.i.**

Results: **A total of 44 prospective clinical studies were included in the systematic review, of which 18 studies were subjected to meta-analysis. The pooled prevalence of gut barrier dysfunction was 59 (95 per cent c.i. 48 to 70) per cent; the prevalence was not significantly affected by disease severity, timing of assessment after hospital admission or type of test used, but showed a statistically significant association with age. Overall, nine of 13 randomized clinical trials reported a significant improvement in gut barrier function following intervention compared with the control group, but only three of six studies that used standard enteral nutrition reported a statistically significant improvement in gut barrier function after intervention.**

Conclusion: **Gut barrier dysfunction is present in three of five patients with acute pancreatitis, and the prevalence is affected by patient age but not by disease severity. Clinical studies are needed to evaluate the effect of enteral nutrition on gut function in acute pancreatitis.**

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Introduction

The gastrointestinal tract has been considered an innocent bystander that is subjected to collateral injury in critical illness. The reflex splanchnic vasoconstriction to preserve the perfusion of vital organs results in ischaemic injury, and resuscitation promotes reperfusion injury[1,2]. These events may contribute to the systemic inflammatory response and eventual organ dysfunction[3]. A critical event with the injury to the intestine is the loss of barrier function, increased permeability, and translocation of luminal bacteria and toxins to the portal venous circulation and mesenteric lymph[4].

Pancreatic infection and organ failure are determinants of severity in acute pancreatitis[5]. Gut barrier dysfunction and increased bacterial translocation are implicated in the development of secondary infection, sepsis, multiple organ failure, and death in acute pancreatitis[6]. Studies have shown that microorganisms responsible for sepsis and pancreatic infection are generally enteric in origin[2,7]. Dysfunction of the gut barrier and the subsequent translocation of toxins, bacteria and enteric microflora into the portal venous and lymphatic systems may cause multiple organ dysfunction syndrome[8]. Many interventions have been investigated in patients with acute pancreatitis with the aim of improving clinical outcomes, but only enteral nutrition has been shown to produce clear clinical benefits in patients with acute pancreatitis as it reduces the risk of developing both pancreatic infections and multiple organ dysfunction syndrome[9–12].

Gut barrier dysfunction is characterized by damage to the gut epithelium and intestinal tight junctions, resulting in increased intestinal permeability[7,13] and compromise of the protective role of the gut barrier[14,15]. However, the permeability pathways, the effect of interventions on gut barrier function, and the implications of gut barrier dysfunction in the pathophysiology of acute pancreatitis

are complex and not well understood. Loss of gut barrier integrity and increased gut barrier dysfunction have been observed in patients with acute pancreatitis, but there is discrepancy in the prevalence of gut barrier dysfunction in clinical studies[6,16–18]. Various interventions aimed at preserving gut barrier function and integrity have been evaluated and are centred mainly on optimizing nutritional management in patients. Although the effect of enteral nutrition in reducing gut barrier dysfunction in animal studies has been coherent, there has been discrepancy amongst clinical studies on the effect of enteral nutrition in reducing gut barrier dysfunction and bacterial translocation[19–23]. Some of the issues with clinical studies that might have contributed to the conflicting evidence include the heterogeneity of tests used to assess gut barrier function, the variability in disease severity, and the variation in timing of assessment used in different clinical studies.

The aim of the present study was to conduct a comprehensive systematic literature review of the best available evidence on gut barrier dysfunction in patients with acute pancreatitis, and to determine the prevalence of gut barrier dysfunction in patients with acute pancreatitis, the effect of different co-variables, as well as the impact of various therapeutic modalities.

Methods

The reporting of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24] and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist[25].

Study identification and selection

An electronic literature search of three major biomedical databases, PubMed, Embase and Scopus, was conducted from the earliest available date to 1 January 2014, with no geographical restrictions. The search strategy, by database, is provided in *Appendix S1* (supporting information). Titles and abstracts were screened for relevance to the study. Full-text articles were obtained for all relevant studies and were appraised for eligibility of inclusion. Study identification, screening and selection were conducted independently by two reviewers, and any discrepancies were resolved by discussion with the senior author.

Eligibility criteria for study selection

For a study to be included, the following criteria needed to be met: design (prospective observational or interventional study); population (adult patients with acute pancreatitis, aged at least 18 years); outcome (gut barrier function assessed). A study was excluded if the full-text article was not in English or the sample size was fewer than ten patients. Studies were also excluded if they used blood cultures as the only method of assessing gut barrier function.

Data extraction

Qualitative and quantitative data from all the included studies were extracted independently by two reviewers and entered into a standard data extraction form. The following data were extracted for each study: author(s); year of publication; country; study design; number of patients with acute pancreatitis; severity of acute pancreatitis; criteria for assessment of disease severity; test(s) of gut barrier function used; number of patients undergoing test; number of patients with gut barrier dysfunction; duration of disease onset before hospital admission; timing of assessment of gut barrier function after hospital admission; sex; age; body mass index; aetiology (alcohol, biliary, other); intervention(s); significance of interventions. For extraction of data on gut barrier dysfunction, only data from discrete individuals were included, and data from repeated measures taken from the same patient were excluded. For studies with sequential assessment of gut barrier function, only the timing of the earliest assessment was extracted, unless prevalence results were combined over sequential assessments.

Quality assessment

Methodological quality of the included studies was assessed independently by two reviewers using the Newcastle–Ottawa scale[26]. Quality assessment was stratified by study design, and an interventional study was assessed using similar criteria as a prospective cohort study, owing to the nature of the extracted data from the interventional studies. Cohort studies were assessed on the following categories: selection of the cohorts (0–4 points), comparability of the cohorts (0–2 points), and outcome assessment (0–3 points). Case–control studies were assessed on the following categories: selection of the cases and controls (0–4 points), comparability of cases and controls (0–2 points), and ascertainment of the exposure (0–3 points). Each study could be awarded a maximum of nine points, and studies that were awarded seven or more points were rated as having high methodological quality[27,28].

Data synthesis and statistical analysis

The pooled prevalence of gut barrier dysfunction was the primary outcome of interest in the meta-analysis.

Data from the included studies were combined to determine the pooled prevalence of gut barrier dysfunction and the associated 95 per cent c.i. The medical statistical software StatsDirect version 3.0.97 was used[29]. When studies used the same patient population, only the study that reported the most conservative result was included. For studies that used more than one test to assess gut barrier function, or used sequential assessment of gut barrier function, the most conservative result was included in the pooled analysis. For interventional studies, only baseline data (before commencement of the intervention) were included in the pooled analysis of prevalence. The effect of interventions was assessed by the comparison of gut barrier function in the intervention group *versus* the control group postintervention.

Subgroup analyses were performed according to disease severity (mild *versus* severe), study location and study design (cohort *versus* case–control), where randomized clinical trials were analysed as cohort studies. Sensitivity analyses constrained to assessment of gut barrier function within 24, 48 and 72 h of hospital admission, constrained to particular criteria for severity assessment, and constrained to assessment of gut barrier dysfunction using a particular test were conducted (if data were available from 2 or more studies). If a study used more than one test of gut barrier function, prevalence data from all the reported tests were included in sensitivity analyses constrained to different tests used. The different tests used to assess gut barrier function were classified into three major groups: assessments of gut epithelial barrier integrity; functional assessments of the gut barrier; and assessments of bacterial translocation[14]. Assessments of gut epithelial barrier integrity were subclassified into tests of enterocyte damage or paracellular barrier integrity loss[14]. Functional assessments of the gut barrier were subclassified into tests that utilize active or passive measurements[14].

Statistical heterogeneity between the studies was assessed using the Cochran's Q for statistical significance[30] and the I^2 statistic for quantifying heterogeneity[30,31]. Statistical significance was set at $P < 0{\cdot}100$ using Cochran's Q, and low, moderate and high statistical heterogeneity was set at I^2 values of 25, 50 and 75 per cent respectively[30]. The analysis was performed using the DerSimonian–Laird random-effects method to yield the most conservative results[32,33]. Potential for publication bias was assessed by visual inspection of funnel plot assymetry and by using the Begg[34], Egger[35] and Harbord[36] tests, with statistical significance set at $P < 0{\cdot}050$[37].

Metaregression analyses were performed using the metafor package in R 3.0.2 statistical software (http://www.metafor-project.org/doku.php) to investigate the possible confounding effect of the following factors: sex, age, biliary aetiology and disease severity[33,38]. Statistical significance in the metaregression analyses was set at $P < 0{\cdot}100$[39,40]. A random-effects model was used for the analyses to yield the most conservative results[33]. Each co-variable was fitted both univariably into individual models and also combined into a single model, and the results from the two methods were compared[33,40]. For the metaregression analyses, only the mean age was used and, where data were available, this was estimated using the values of the median, low end and high end of the range[41]. If sample size data were available, the mean ages of different patient groups within a study were combined to give a single mean for the metaregression analyses.

Results

A total of 3584 records were identified through the initial literature search and 90 potentially relevant full-text articles were retrieved and assessed for eligibility (*Fig. 1*). Forty-six articles were excluded at this stage, yielding a total of 44 studies[6,12,16–18,21–23,42–77] that were included in the systematic review. There were 13 randomized clinical trials and 31 observational studies, which included both prospective cohort and case–control studies (*Table 1*). Twenty-seven studies were conducted in Europe, and the remaining 17 studies in Asia. The 44 studies encompassed a total of 2611 patients with acute pancreatitis, of whom 2094 patients underwent assessment of gut barrier function. The baseline characteristics of individuals in the included studies are presented in *Table S1* (supporting information).

Assessment of methodological quality and publication bias

Overall, 42 of the 44 studies were of high methodological quality (*Table S2*, supporting information). The most common reasons for not scoring a point were potential selection biases and inadequate control for possible confounding factors, such as timing of assessment, severity of acute pancreatitis and age. There was no evidence of publication bias by visual inspection of funnel plot assymetry, and by using the Begg ($P = 0{\cdot}822$), Egger ($P = 0{\cdot}986$) or Harbord ($P = 0{\cdot}220$) test.

Tests used to assess gut barrier function

A total of 14 different tests were used to assess gut barrier function in the included studies (*Table 2*). Of the 14 tests used, three assessed gut epithelial barrier integrity, seven were functional assessments of the gut barrier and four

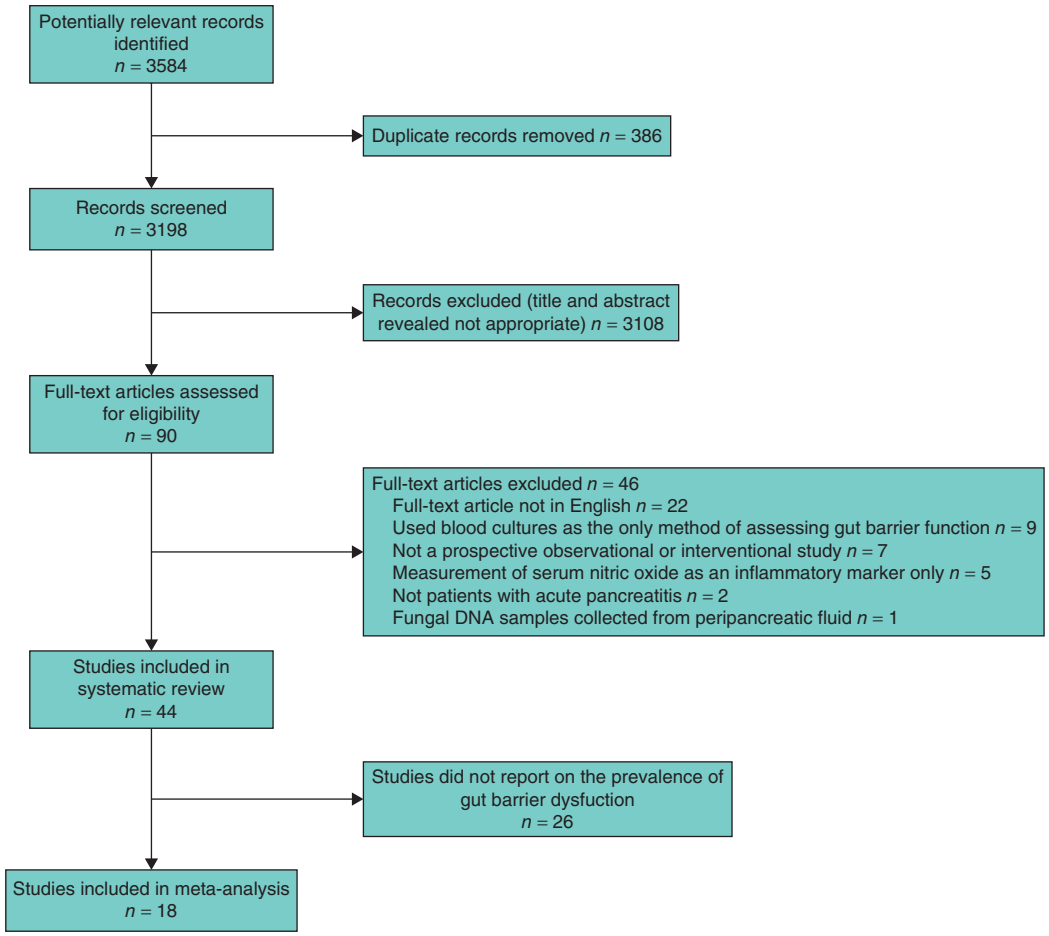

Fig. 1 Flow diagram of the study selection process

assessed bacterial translocation. Of the 44 included studies, five assessed gut epithelial barrier integrity, 37 studies utilized functional assessments of the gut barrier and 25 assessed bacterial translocation (*Table 1*). Twenty-three of the 44 included studies measured endotoxins, 20 measured endogenous antiendotoxin core antibodies and 11 measured the lactulose/mannitol ratio; these were the three most frequently used tests. Each study used between one and four tests to assess gut barrier function, with a median of 2 tests per study. The 44 studies spanned a total of three decades. *Fig. 2* depicts the total frequency of tests used within each 5-year interval, as well as the frequency within each of the three major groups of tests.

Prevalence of gut barrier dysfunction

Eighteen[6,17,18,42–48,51–53,55,57,63,64,75] of the 44 studies reported data on the prevalence of gut barrier dysfunction in patients with acute pancreatitis, encompassing a total of 743 patients, 573 of whom had assessment of gut barrier function (*Table 1*). The pooled prevalence of gut barrier dysfunction in patients with acute pancreatitis, using the most conservative test result from each study, was 59 (95 per cent c.i. 48 to 70) per cent (*Fig. 3*), in the presence of high statistical heterogeneity ($I^2 = 87$ per cent, $P < 0{\cdot}001$).

A number of prespecified subgroup and sensitivity analyses were carried out to investigate the effect of possible confounders. Subgroup analysis of patients with mild acute pancreatitis included a total of 11 studies[6,17,45,46,48,53,55,57,63,64,75] comprising 247 patients who underwent assessment of gut barrier function. The pooled prevalence of gut barrier dysfunction in patients with mild acute pancreatitis was 47 (95 per cent c.i. 30 to 64) per cent (*Fig. S1A*, supporting information), with no reduction in statistical heterogeneity ($I^2 = 87$ per cent, $P < 0{\cdot}001$). Twelve studies[17,44–48,53,55,57,63,64,75], comprising a total of 204 patients who underwent assessment of gut barrier function, provided data for subgroup analysis of patients

Table 1 Characteristics of included studies

Reference	Year	Country	Study design	No. of patients with acute pancreatitis	No. of patients undergoing test	Tests of gut barrier function used	Timing of assessment of gut barrier function
Foulis *et al.*[42]	1982	UK	Prospective cohort	24	24	Endotoxin*	Daily¶
Beger *et al.*[43]	1988	Germany	Prospective cohort	95	30	Endotoxin	Preoperative
Exley *et al.*[44]	1992	UK	Prospective cohort	38	37	Endotoxin	≤ 24 h¶
Curley *et al.*[45]	1993	UK	Prospective case–control	29	28	EndoCAb, endotoxin	≤ 48 h¶
Windsor *et al.*[46]	1993	UK	Prospective cohort	33	33	EndoCAb, endotoxin	≤ 24 h¶
Wig *et al.*[47]	1998	India	Prospective cohort	14	14	Endotoxin	Consecutively over 2 or 4 days¶
Windsor *et al.*[12]	1998	UK	RCT	34	34	EndoCAb	≤ 48 h¶
Ammori *et al.*[48]	1999	UK	Prospective case–control	85	64	EndoCAb, endotoxin, PEGs	≤ 24 h¶
Soong *et al.*[49]	1999	UK	Prospective cohort	19	19	EndoCAb, endotoxin	≤ 12 h¶
Buttenschoen *et al.*[50]	2000	Germany	Prospective case–control	25	25	EndoCAb, endotoxin	≤ 24 h¶
Juvonen *et al.*[16]	2000	Finland	Prospective case–control	23	23	L/R, multisugar probes	≤ 48 h¶
Powell *et al.*[51]	2000	UK	RCT	27	22	EndoCAb, L/R	≤ 24 h¶
Zhang *et al.*[52]	2001	China	Prospective case–control	13	13	DNA/RNA†	n.r.
Bose *et al.*[53]	2002	India	Prospective cohort	20	20	EndoCAb, endotoxin	≤ 72 h¶
Martínez *et al.*[54]	2002	Spain	Prospective cohort	19	19	EndoCAb, endotoxin	≤ 24 h¶
McNaught *et al.*[55]	2002	UK	Prospective cohort	59	27	L/R	≤ 72 h¶
Ammori *et al.*[56]	2003	UK	Prospective cohort	72‡	72	EndoCAb, endotoxin	≤ 24 h¶
Ammori *et al.*[57]	2003	UK	Prospective cohort	60‡	52	EndoCAb, endotoxin, PEGs	≤ 24 h¶
Ammori *et al.*[17]	2003	UK	Prospective case–control	26	26§	EndoCAb, endotoxin, DNA/RNA, PEGs	≤ 24 h¶
Giamarellos-Bourboulis *et al.*[18]	2003	Greece	Prospective cohort	33	33	Endotoxin	≤ 24 h¶
Gupta *et al.*[22]	2003	UK	RCT	17	17	EndoCAb	≤ 24 h¶
Rahman *et al.*[58]	2003	UK	Prospective case–control	61‡	61	EndoCAb, I-FABP, PEGs	≤ 72 h#
Rahman *et al.*[59]	2003	UK	Prospective case–control	65‡	65	EndoCAb, NO, PEGs	≤ 48 h#
Zhao *et al.*[60]	2003	China	RCT	96	96	Endotoxin, L/M	≤ 24 h¶
Penalva *et al.*[61]	2004	Spain	Prospective case–control	68	68	EndoCAb, L/M	≤ 72 h#
Rahman *et al.*[62]	2004	UK	Prospective case–control	320	46	Reduced GSH	≤ 24 h#
De Madaria *et al.*[63]	2005	Spain	Prospective cohort	31	31	DNA/RNA	≤ 48 h¶
Eckerwall *et al.*[21]	2006	Sweden	RCT	48	40	EndoCAb, PEGs	≤ 24 h¶
Nagpal *et al.*[64]	2006	UK	Prospective case–control	46	45	L/M	Days 1, 4, 7¶
Liu *et al.*[6]	2008	China	Prospective case–control	62	26	D-Xylose, endotoxin, L/M	≤ 72 h#
Qin *et al.*[65]	2008	China	RCT	74	71	L/R	≤ 24 h¶
Besselink *et al.*[66]	2009	Netherlands	RCT	141	115	I-FABP, NO, PEGs	≤ 72 h¶
Chen *et al.*[67]	2010	China	RCT	40	40	Endotoxin, L/M	≤ 24 h¶
Pan *et al.*[68]	2010	China	Prospective cohort	32	32	I-FABP, L/M	≤ 24 h¶
Zhang *et al.*[69]	2010	China	RCT	63	63	Endotoxin, F-actin, serum DAO	Preintervention
Sharma *et al.*[70]	2011	India	RCT	50	40	EndoCAb, L/M	≤ 24 h¶
Shen *et al.*[71]	2011	China	Prospective cohort	72	72	Endotoxin	≤ 24 h¶
Koh *et al.*[72]	2012	Korea	Prospective cohort	87	87	Endotoxin, L/M	≤ 24 h¶
Pynnönen *et al.*[73]	2012	Finland	Prospective cohort	30	27	Rectal luminal lactate	≤ 24 h¶
Sharma *et al.*[74]	2012	India	Prospective case–control	31	31	EndoCAb, L/M	≤ 24 h¶
Singh *et al.*[23]	2012	India	RCT	78	55	EndoCAb, L/M	≤ 48 h¶
Li *et al.*[75]	2013	China	Prospective case–control	48	48	DNA/RNA	Days 4, 5**
Wang *et al.*[76]	2013	China	RCT	183	183	Endotoxin	Preintervention
Zhao *et al.*[77]	2013	China	RCT	120	120	Endotoxin, L/M	≤ 24 h¶

*Serum endotoxin; †bacterial DNA or RNA by PCR; ‡patients drawn from a similar patient group; §disregarded results from PCR owing to substances inhibitory to the amplification of DNA in two-fifths of patients; ¶after hospital admission; #after onset of acute pancreatitis; **after diagnosis of acute pancreatitis. EndoCAb, endogenous antiendotoxin core antibodies; RCT, randomized clinical trial; PEGs, polyethylene glycols; L/R, lactulose/rhamnose ratio; n.r., not reported; I-FABP, intestinal fatty acid-binding protein; NO, nitric oxide; L/M, lactulose/mannitol ratio; GSH, reduced glutathione; DAO, diamine oxidase.

Table 2 Tests used to assess gut barrier function

Classification	Subclassification	Tests	Frequency of tests used	Study design*	Pooled prevalence of gut barrier dysfunction (%)†	Heterogeneity
Assessments of gut epithelial barrier integrity	Enterocyte damage	I-FABP	3	Observational (2) Interventional (1)	n.e.	
		Reduced GSH	1	Observational (1)	n.e.	
	Paracellular barrier integrity loss	F-actin	1	Interventional (1)	n.e.	
Functional assessments of gut barrier	Active measurements	L/M ratio	11	Observational (6) Interventional (5)	79 (61, 92) (2)	$P = 0{\cdot}091$
		PEGs	7	Observational (5) Interventional (2)	n.e.	
		L/R ratio	4	Observational (2) Interventional (2)	66 (44, 84) (2)	$P = 0{\cdot}116$
		D-Xylose	1	Observational (1)	n.e.	
		Multisugar probes	1	Observational (1)	n.e.	
		Serum DAO	1	Interventional (1)	n.e.	
	Passive measurements	Endotoxins	23	Observational (18) Interventional (5)	57 (43, 71) (11)	$I^2 = 88\%$, $P < 0{\cdot}001$
Assessments of bacterial translocation		EndoCAb	20	Observational (14) Interventional (6)	56 (15, 93) (2)	$P < 0{\cdot}001$
		DNA/RNA‡	4	Observational (4)	46 (17, 77) (3)	$I^2 = 89\%$,
		NO	2	Observational (1) Interventional (1)	n.e.	$P < 0{\cdot}001$
		Rectal luminal lactate	1	Observational (1)	n.e.	

*Values in parentheses are number of studies; †values in parentheses are 95 per cent c.i. followed by number of studies. ‡Bacterial DNA or RNA by PCR. I-FABP, intestinal fatty acid-binding protein; n.e., not estimable; GSH, reduced glutathione; L/M, lactulose/mannitol; PEGs, polyethylene glycols; L/R, lactulose/rhamnose; DAO, diamine oxidase; EndoCAb, endogenous antiendotoxin core antibodies; NO, nitric oxide.

with severe acute pancreatitis. The pooled prevalence of gut barrier dysfunction in patients with severe acute pancreatitis was 59 (47 to 70) per cent (*Fig. S1B*, supporting information), in the presence of moderate statistical heterogeneity ($I^2 = 66$ per cent, $P < 0{\cdot}001$). For the studies that used functional assessments of the gut barrier, subgroup analysis of mild acute pancreatitis[6,17,45,46,48,53,55,57,64] resulted in a pooled prevalence of gut barrier dysfunction of 51 (32 to 70) per cent, in the presence of high statistical heterogeneity ($I^2 = 83$ per cent, $P < 0{\cdot}001$), whereas severe acute pancreatitis[17,44–48,53,55,57,64] resulted in a pooled prevalence of gut barrier dysfunction of 60 (47 to 72) per cent, in the presence of moderate statistical heterogeneity ($I^2 = 52$ per cent, $P = 0{\cdot}028$). For the studies that used assessments of bacterial translocation, subgroup analysis of mild acute pancreatitis[45,46,63,75] resulted in a pooled prevelance of gut barrier dysfunction of 21 (10 to 40) per cent, in the presence of low statistical heterogeneity ($I^2 = 40$ per cent, $P = 0{\cdot}174$), whereas severe acute pancreatitis[45,46,63,75] resulted in a pooled prevalence of gut barrier dysfunction of 41 (18 to 69) per cent, in the presence of high statistical heterogeneity ($I^2 = 79$ per cent, $P = 0{\cdot}003$).

Subgroup analysis of cohort studies[17,18,42–44,46,47,51,53,55,57,63] resulted in a pooled prevelance of gut barrier dysfunction of 61 (95 per cent c.i. 48 to 73) per cent, with no reduction in statistical heterogeneity ($I^2 = 84$ per cent, $P < 0{\cdot}001$). Subgroup analysis of case–control studies[6,45,48,52,64,75] resulted in a pooled prevalence of gut barrier dysfunction of 54 (32 to 76) per cent, with no reduction in statistical heterogeneity ($I^2 = 91$ per cent, $P < 0{\cdot}001$). Subgroup analysis of studies performed in Europe resulted in a pooled prevalence of gut barrier dysfunction of 53 (41 to 66) per cent, with no reduction in statistical heterogeneity ($I^2 = 83$ per cent, $P < 0{\cdot}001$). Subgroup analysis of studies performed in Asia resulted in a pooled prevalence of gut barrier dysfunction of 74 (60 to 84) per cent, in the presence of low statistical heterogeneity ($I^2 = 46$ per cent, $P = 0{\cdot}114$).

Sensitivity analyses constrained to assessment of gut barrier function within 24 h[17,18,44,46,48,51,57], 48 h[17,18,44–46,48,51,57,63] and 72 h[6,17,18,44–46,48,51,53,55,57,63] of hospital admission resulted in the pooled prevalence of gut barrier dysfunction of 59 (95 per cent c.i. 41 to 76), 49 (32 to 67) and 56 (41 to 71) per cent respectively. Sensitivity analysis excluding studies where the criteria for assessment of disease severity were not reported resulted in a pooled prevalence of gut barrier dysfunction of 53 (41 to 66) per cent, in the presence of high statistical heterogeneity ($I^2 = 83$ per cent, $P < 0{\cdot}001$). Sensitivity analysis constrained to studies using the 1992 Atlanta

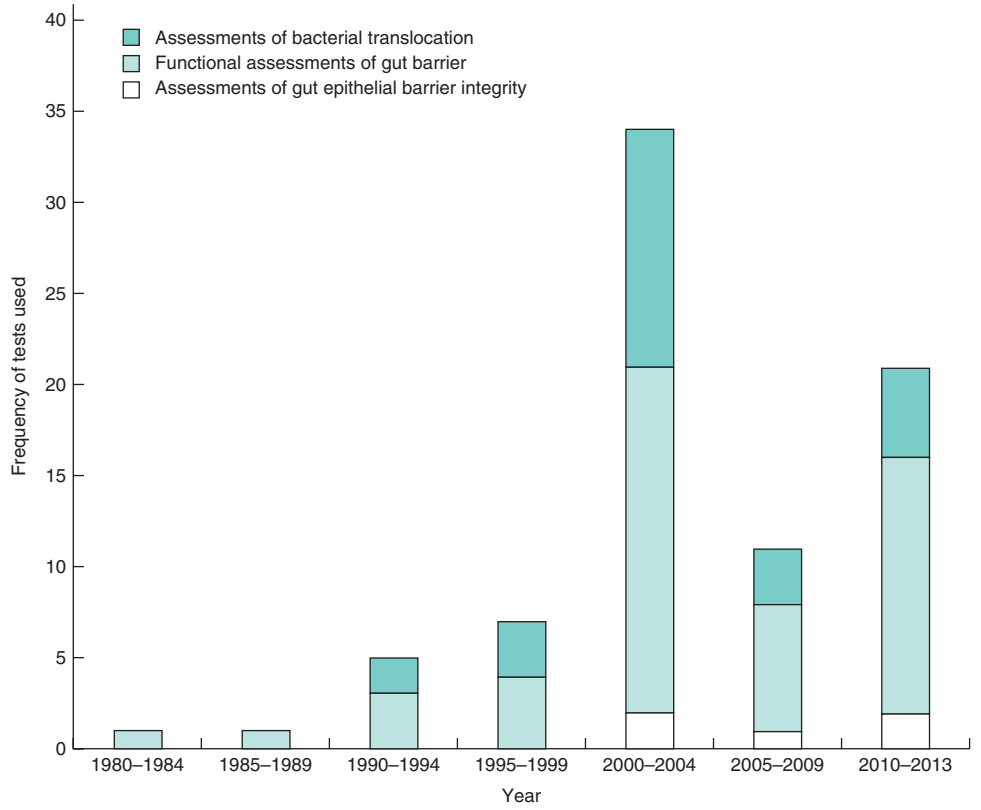

Fig. 2 Tests of gut barrier dysfunction used in patients with acute pancreatitis over the past three decades

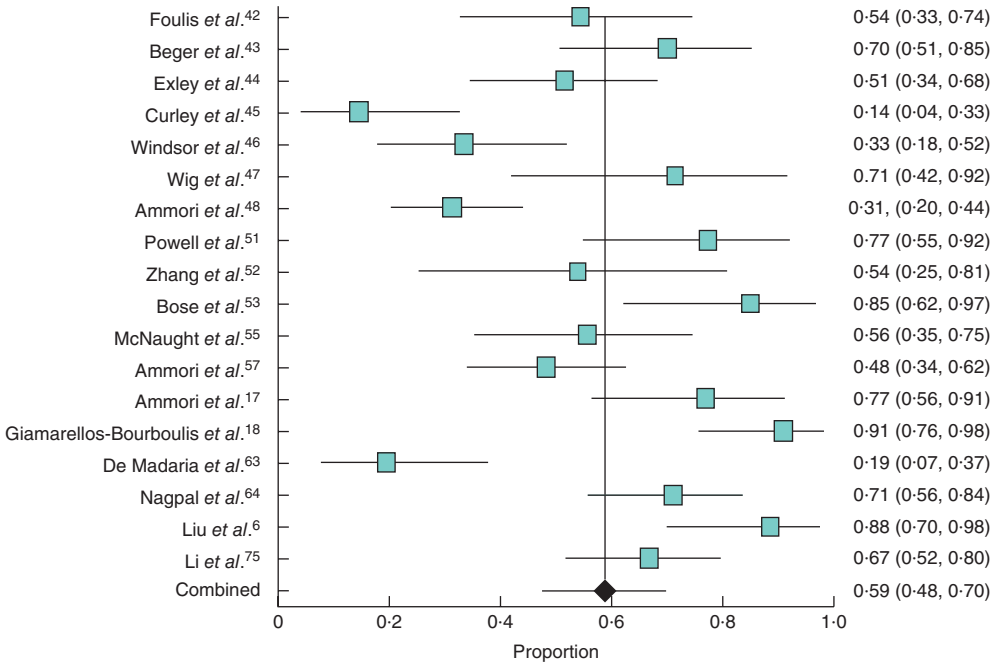

Fig. 3 Forest plot showing prevalence of gut barrier dysfunction in patients with acute pancreatitis. Proportions with 95 per cent c.i. are shown

Table 3 Results of metaregression analyses

	Overall	Sex*	Age*	Biliary aetiology†	Severity‡
Each co-variable fitted into individual models					
Estimate	n.e.	0·005 (–0·004, 0·015)	–0·012 (–0·026, 0·002)	–0·000 (–0·007, 0·007)	0·002 (–0·003, 0·007)
P	n.e.	0·273	0·090*	0·951	0·484
All co-variables fitted into one model					
Estimate	n.e.	0·000 (–0·011, 0·011)	–0·016 (–0·033, 0·001)	0·000 (–0·006, 0·007)	0·002 (–0·003, 0·007)
P	0·275	1·000	0·058	0·896	0·423

Values in parentheses are 95 per cent c.i. *All 18 studies included in model fitting; †17 studies included in model fitting as co-variable not reported in one study; ‡15 studies included in model fitting as co-variable not reported in three studies. n.e., Not estimable.

classification[78] resulted in the pooled prevalence of gut barrier dysfunction of 60 (43 to 75) per cent.

Sensitivity analyses were also carried out to investigate the effect of using different tests to assess gut barrier function. Sensitivity analysis constrained to assessment of gut barrier function by measurement of serum endotoxins included a total of 11 studies[17,18,42–48,53,57], comprising 361 patients who underwent assessment of gut barrier function (*Table 1*). The pooled prevalence of gut barrier dysfunction was 57 (95 per cent c.i. 43 to 71) per cent, in the presence of high statistical heterogeneity ($I^2 = 88$ per cent, $P < 0·001$) (*Table 2*). Three studies[52,63,75], comprising a total of 92 patients, provided data for sensitivity analysis constrained to assessment of gut barrier function by measurement of bacterial DNA or RNA in blood, as detected by PCR (*Table 1*). The pooled prevalence of gut barrier dysfunction was 46 (17 to 77) per cent, in the presence of high statistical heterogeneity ($I^2 = 89$ per cent, $P < 0·001$) (*Table 2*). Sensitivity analyses constrained to assessment of gut barrier function by measurement of endogenous antiendotoxin core antibodies[45,46], lactulose/mannitol ratio[6,64] and lactulose/rhamnose ratio[51,55] resulted in the pooled prevalence of gut barrier dysfunction of 56 (15 to 93), 79 (61 to 92) and 66 (44 to 84) per cent, with statistical heterogeneity of $P < 0·001$, $P = 0·091$ and $P = 0·116$ respectively (*Table 2*).

Metaregression analyses showed that mean age of the patients had a statistically significant association with the prevalence of gut barrier dysfunction using both methods of model fitting (*Table 3*). The prevalence of gut barrier dysfunction against the mean age for individual studies is presented in *Fig. 4*. The remaining co-variables investigated in the metaregression analyses (sex, aetiology and severity of disease) did not have a statistically significant association with the prevalence of gut barrier dysfunction using either method of model fitting (*Table 3*).

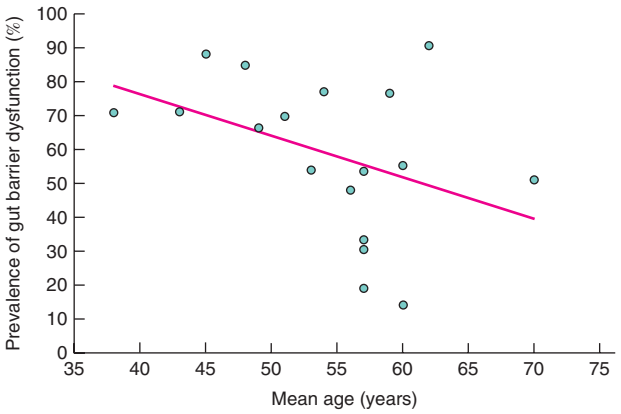

Fig. 4 Prevalence of gut barrier dysfunction against the mean age for individual studies in patients with acute pancreatitis

Effect of interventions on gut barrier function

Thirteen[12,21–23,51,60,65–67,69,70,76,77] of the 44 included studies were randomized clinical trials. The types of intervention used were standard enteral nutrition (standard enteral nutrition formulas without specific immunomodulating nutrients) (6 studies[12,21–23,51,60]), advanced enteral nutrition (enteral nutrition in combination with probiotics or ecoimmunonutrition) (5 studies[65,66,70,76,77]), continuous blood purification treatment (1 study[69]) and traditional Chinese medicine (1 study[67]). Overall, nine[12,22,60,65–67,69,76,77] of the 13 randomized clinical trials reported a significant improvement in gut barrier function postintervention compared with the control group ($P < 0·050$). Three[12,22,60] of the six studies that used standard enteral nutrition reported a significant improvement in gut barrier function ($P < 0·050$), as measured by serum endotoxins, endogenous antiendotoxin core antibodies and lactulose/mannitol ratio. However, the remaining three studies[21,23,51] that used standard enteral nutrition reported no significant difference in gut barrier function, as measured by endogenous antiendotoxin core antibodies, polyethylene glycols, lactulose/mannitol ratio and lactulose/rhamnose ratio. Four[65,66,76,77] of the five studies that used advanced enteral nutrition showed a significant improvement in gut barrier function ($P < 0·050$), as measured by serum endotoxins, lactulose/mannitol ratio, lactulose/rhamnose ratio and nitric oxide. The studies

that used continuous blood purification treatment[69] and traditional Chinese medicine[67] both showed a significant improvement in gut barrier function ($P < 0{\cdot}050$), as measured by serum endotoxins and lactulose/mannitol ratio.

Discussion

This study demonstrates that gut barrier dysfunction is present in three of five patients with acute pancreatitis, and that the prevalence is not significantly affected by disease severity or timing of assessment after hospital admission, but shows a statistically significant association with age. A total of 14 different tests, conventionally classified into assessments of gut epithelial barrier integrity, functional assessments of the gut barrier and assessments of bacterial translocation, have been used to assess gut barrier function in patients with acute pancreatitis[14]. This study shows that the prevalence of gut barrier dysfunction is approximately the same over the three groups of tests and not significantly affected by the type of test used.

One of the important clinical findings in this study is that gut barrier dysfunction is common in patients with acute pancreatitis and that there is no statistically significant difference between the prevalence of gut barrier dysfunction in patients with mild and severe acute pancreatitis, in both subgroup and metaregression analysis. This suggests that gut barrier dysfunction may be a characteristic of the disease, rather than a condition that develops with disease progression. However, limitations of the 1992 Atlanta classification of acute pancreatitis severity[78] may have influenced the results, and it remains to be seen whether the results observed in the present study will also be seen when modern, more granular, classifications of severity[79,80] are employed. Further, prespecified sensitivity analyses show that there is no statistically significant difference between the prevalence of gut barrier dysfunction within 24, 48 and 72 h after hospital admission. A possible explanation for this result is the varying duration between disease onset and hospital admission. However, nine[6,18,47,48,51,53,57,64,75] of the 18 studies in the meta-analysis reported on the duration of disease at the time of hospital admission, and only one of these studies[47] reported delayed hospital admission of more than 72 h after disease onset. Prolonged duration of disease before hospital admission may have resulted in assessment of gut barrier function during the restitution phase of the gut barrier[61], leading to an underestimation of the pooled prevalence of gut barrier dysfunction. Intra-abdominal hypertension is also thought to be associated with gut barrier dysfunction, but the literature lacks consensus on the cause–effect relationship of intra-abdominal hypertension and gut barrier dysfunction in human studies[81–83]. Only five[44,46–48,53] of the 44 included studies specifically investigated the association between gut barrier dysfunction and infected pancreatic necrosis and/or mortality. Future studies investigating gut barrier function in acute pancreatitis should include only a short duration of disease (48 h or less) as a criterion for patient recruitment, in an attempt to capture patients with a similar phase of disease progression, as well as investigate the association between gut barrier dysfunction and clinical endpoints other than severity of acute pancreatitis.

The metaregression analyses show that mean age of the patient has a statistically significant association with the prevalence of gut barrier dysfunction. The estimate using the combined model shows that, in the presence of the other co-variables, there is a 2 per cent decrease in the prevalence of gut barrier dysfunction for every 1-year increase in patient age. This suggests that patient age may have a significant impact on the prevalence of gut barrier dysfunction and might have been a confounding variable in past clinical studies of gut barrier function. This finding provides justification for future studies to enrol patients within a particular age group or to control for patient age in the analyses.

A wide variety of tests of gut barrier function exists. This provides impetus for the development of improved tests and the standardization of existing tests in order to improve the clinical assessment of gut barrier dysfunction and to improve the comparability of studies. The prevalence of gut barrier dysfunction using the PCR technique as a measure of bacterial translocation was comparable to estimates obtained using other tests of gut barrier function. In fact, sensitivity analyses showed that PCR resulted in the lowest prevalence of gut barrier dysfunction compared with the other tests. This is in contrast to the suggestion that use of PCR to detect bacterial DNA in the circulation is too sensitive to be a useful marker of bacterial translocation in acute pancreatitis[84].

Only half (three of six) of the studies that used standard enteral nutrition reported a statistically significant improvement in gut barrier function postintervention. This contrasts with high-quality evidence indicating that enteral nutrition has clear clinical benefits in patients with acute pancreatitis, which is generally attributed to the improvement of gut barrier function[8–12]. There are two potential explanations. The first is that standard enteral nutrition exerts its beneficial effect in acute pancreatitis independent of any significant improvement in gut barrier function. The second is that standard enteral nutrition does improve gut barrier function but some technical

limitations in the clinical studies and possible confounding variables, as discussed previously, might have overshadowed its beneficial effect. Further, four of the five studies that used advanced enteral nutrition reported a significant improvement in gut barrier function postintervention. In light of the evidence from the present study, there is justification for further research to understand better the role of enteral nutrition in the pathophysiology of acute pancreatitis and to evaluate the benefit of advanced enteral nutrition in the mitigation of gut barrier dysfunction.

There are further points to consider when interpreting the results of this study. First, a wide variety of tests have been used, and they each investigate different aspects of gut barrier dysfunction. This heterogeneity of the tests may be a possible limitation for the pooled estimate. However, the present study included only validated tests for measuring the prevalence of gut barrier dysfunction[14]. For example, tests of bacterial DNA or RNA using blood cultures were excluded, as recent studies have reported this to be an insensitive method of detection[63,75]. In addition, prespecified sensitivity analyses constrained to the assessment of gut barrier function using different tests showed no statistically significant difference between the prevalence of gut barrier dysfunction. Second, the high statistical heterogeneity between the studies may be a possible limitation for the pooled estimate and the conclusions that can be drawn from the meta-analysis. However, a random-effects model was used in the present analyses to yield the most conservative estimate of the pooled prevalence[33,85]. In addition, the most conservative result was taken for each study, so the probability of overestimating the prevalence of gut barrier dysfunction is low. Furthermore, an increase in statistical power was achieved through the use of meta-analytical techniques, as this is known to result in a more reliable estimate compared with individual primary studies of low statistical power[25,32,33]. Third, the present analysis included observational studies, which may have been subject to confounding variables. To counter this, a number of prespecified subgroup, sensitivity and metaregression analyses using two different methods of model fitting were performed to investigate the effect of possible confounding variables on the prevalence of gut barrier dysfunction. Fourth, by including only studies that have full-text articles in English, the possibility of language bias cannot be excluded. However, given that 27 of the 44 studies were conducted in a country where English is not the official language and the diverse geographical distribution of the included studies, it is unlikely that language of publication would have a significant effect on the results presented here. In addition, exclusion of non-English-language publications has been shown to have little effect on the summary estimates, and studies published in English tend to include more participants, have higher methodological quality and produce more conservative estimates[86]. Finally, the possibility of publication bias cannot be excluded. However, visual inspection of funnel plot symmetry and the use of three different statistical tests revealed no statistical evidence of publication bias.

Disclosure

The authors declare no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1 Search strategy, by database (Word document)

Table S1 Baseline characteristics of individuals in included studies (Word document)

Table S2 Methodological quality assessment of included studies based on the Newcastle–Ottawa scale (Word document)

Fig. S1 Forest plot for prevalence of gut barrier dysfunction in patients with **A** mild and **B** severe acute pancreatitis (Word document)