SYSTEMATIC REVIEWS

Intra-abdominal pressure: Time ripe to revise management guidelines of acute pancreatitis?

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Abstract

AIM: To systematically review evidence on pathophysiology of intra-abdominal pressure (IAP) in acute pancreatitis (AP) with its clinical correlates.

METHODS: Systematic review of available evidence in English literature with relevant medical subject heading terms on PubMed, Medline and Scopus with further search from open access sources on internet as suggested by articles retrieved.

RESULTS: Intra-abdominal hypertension (IAH) is increasingly gaining recognition as a point of specific intervention with potential to alter disease outcome and improve mortality in AP. IAH can be expected in at least 17% of patients presenting with diagnosis of AP to a typical tertiary care hospital (prevalence increasing to 50% in those with severe disease). Abdominal compartment syndrome can be expected in at least 15% patients with severe disease. Recent guidelines on management of AP do not acknowledge utility of surveillance for IAP other than those by Japanese Society of Hepato-Biliary-Pancreatic Surgery. We further outline pathophysiologic mechanisms of IAH; understanding of which advances our knowledge and helps to coherently align common observed variations in management related conundrums (such as fluid therapy, nutrition and antibiotic prophylaxis) with potential to further individualize treatment in AP.

CONCLUSION: We suggest that IAP be given its due place in future practice guidelines and that recommendations be formed with help of a broader panel with inclusion of clinicians experienced in management of IAH.

Key words: Intra-abdominal hypertension; Abdominal compartment syndrome; Pancreatitis; Practice guideline

Core tip: Intra-abdominal hypertension is not merely an epiphenomenon but offers a unique point of specific intervention in acute pancreatitis and there is increasing data to show improved mortality with appropriate management. It is frequent and may be observed in at least 50% patients with severe disease. Moreover it acts as confounder in management related issues of fluid therapy, nutritional support and antibiotic prophylaxis; and understanding its pathophysiology coherently explains many dichotomies which presently lowers internal validity of much available evidence. Incorporating surveillance for intra-abdominal pressure in select subgroup of patients may help better tailor individualized treatment to patients with most severe spectrum of disease. Recommendations by World Society of the Abdominal Compartment Syndrome may be followed by practicing clinician to guide decision making.

INTRODUCTION

Reported data from many countries reveals epidemiology of acute pancreatitis (AP) showing an increasing trend, and it enjoys the crown of being the most frequent gastrointestinal diagnosis leading to hospital admissions in the United States[1]. Despite exciting developments in understanding pathogenesis of AP; none of the molecular targets have proved useful in routine clinical practice, frustrating clinicians to rely much on "clinical" rather than "translational" research in managing patients[2]. Intra-abdominal hypertension/Abdominal Compartment Syndrome (IAH/ACS) is increasingly being recognized as a point of specific intervention in AP with attractive potential to alter disease outcomes[3]. This review focuses on the role and importance of Intra-abdominal pressure (IAP) in AP with a critical perspective, which is now gaining recognition as a vital sign specific for abdomen but lacks mention in clinical guidelines on management of AP except recently those by Japanese Society of Hepato-Biliary-Pancreatic Surgery[4,5].

MATERIALS AND METHODS

In August 2015 electronic database search of PubMed, Medline and Scopus was performed from 1985 till 20th August 2015. Medical Subject Headings terms "AP", "severe AP (SAP)", "necrotizing pancreatitis", "fulminant pancreatitis" were combined with Boolean operator "AND" with studies identified by keywords "IAH", and "ACS". References of retrieved articles were further searched as relevant including open access sources from internet.

Statistical analyses

The available studies (in English literature) were heterogeneous in terms of study populations, study criteria and critical definitions of what constituted SAP, IAH and ACS. It was thus not possible to apply meta analytic methods and a descriptive narration of available evidence is being performed.

RESULTS

Historical perspective and epidemiology-confounding by definitions

The general understanding of pancreatitis in the decade beginning 2000 was dominated by concept of conservative management in initial phase of disease with operative intervention (which should be delayed till later part of disease) reserved for infected pancreatic necrosis[6]. Clinicians broadly classified patients with pancreatitis into groups of mild and severe as proposed by Atlanta classification[7]. Yet they recognized a sub group of patients with fulminant disease course which had rapid onset of multiple organ dysfunctions leading to high mortality rates. Clinical similarities between ACS and such patients with SAP lead to initial study on the role of IAH in AP, which was first published in 2002 from Medical academy of Latvia[3]. Authors emphasized the role of monitoring IAP as a prognostic tool as they found no mortality among patients who had IAP < 25 cm H_2O *vs* 36% mortality in group of patients with IAP > 25 cm H_2O. In the same year another group from United States reported experience with emergency abdominal decompression in three patients with fulminant AP and ACS (in early phase of AP) out of which one survived[8]. They remarked that role of ACS and emergency abdominal decompression in early phase of AP should find mention in prevalent surgical literature of those times.

Meanwhile in 2004 The World Society of the ACS (WSACS) was founded[9]. It performed the commendable job of developing consensus statements and evidence based recommendations which culminated in initial set of guidelines and definitions of IAH/ACS in 2004 which are periodically revisited (latest congress in 2015). Importantly they standardized the methodology of IAP measurement (preferably transvesical method, with maximal instillation of 25 cc saline, in supine position, measured at end expiration, with zeroing done at the level of mid axillary line) and also the cut off and definitions of IAH and ACS. IAH is defined by a sustained or repeated pathologic elevation of IAP $\geqslant$ 12 mmHg with grading as follows: Grade I: IAP 12-15 mmHg, Grade II: IAP 16-20 mmHg, Grade III: IAP 21-25 mmHg, Grade IV: IAP > 25 mmHg. ACS is defined as a sustained IAP > 20 mmHg [with or without an Abdominal Perfusion Pressure (APP) < 60 mmHg] that

Table 1 Epidemiology of intra-abdominal hypertension and abdominal compartment syndrome in acute pancreatitis as previously reported in literature *n* (%)

Ref.	IAP monitoring	Definition of IAH	Incidence of IAH (among patients with SAP)	Definition of ACS	Incidence of ACS (among patients with SAP)
Pupelis *et al*[3]	Selected	NA	NA	IAP > 25 mmHg	18 (25)
De Waele *et al*[12]	Selected	IAP > 15 mmHg	21 (78)	NA	NA
Pupelis *et al*[13]	Selected	NA	NA	NA	NA
Keskinen *et al*[14]	Selected	IAP > 12 mmHg	31 (84)	IAP > 20 mmHg with new organ dysfunction	18 (49)
Zhang *et al*[15]	Unselected	IAP > 10 cm H_2O (NA)	68 (76)	NA	NA
Rosas *et al*[16]	Unselected (45 patients)	NA	NA	NA	NA
Chen *et al*[17]	Unselected	IAP > 12 mmHg	44 (59)	IAP > 20 mmHg with new organ dysfunction	20 (27)
Al-Bahrani *et al*[18]	Unselected	IAP > 15 mmHg	11 (61)	IAH with organ dysfunction	10 (56)
Dambrauskas *et al*[19]	Unselected	IAP > 12 mmHg	19 (43)	IAP > 20 mmHg with new organ dysfunction	6 (14)
Mentula *et al*[20]	Unselected (26 patients with ACS)	NA	NA	IAP > 20 mmHg with new organ dysfunction	NA
Ke *et al*[21]	Unselected	IAP > 12 mmHg	36 (62)	IAP > 20 mmHg with new organ dysfunction	7 (12)
Bezmarevic *et al*[22]	Unselected	IAP > 12 mmHg	36 (71) (among patients with AP) 27 (97) (among patients with SAP)	IAP > 20 mmHg with new organ dysfunction	6 (12) (among patients with AP) 6 (21) (among patients with SAP)
Boone *et al*[23]	Selected (12 patients undergoing decompressive laparotomy for ACS)	NA	NA	IAP > 20 mmHg with new organ dysfunction	NA
Davis *et al*[24]	Selected	NA	NA	IAP > 20 mmHg with new organ dysfunction	16 (35)
Bhandari *et al*[25]	Unselected	IAP > 12 mmHg	8 (20) (among patients with AP) 8 (50) (among patients with SAP)	IAP > 20 mmHg with new organ dysfunction	3 (7.5) (among patients with AP) 3 (19) (among patients with SAP)
Aitken *et al*[26]	Unselected	IAP > 12 mmHg	36 (17) (among patients with AP)	NA	NA

IAP: Intra-abdominal pressure; IAH: Intra-abdominal hypertension; ACS: Abdominal compartment syndrome; NA: Not available; AP: Acute pancreatitis; SAP: Severe acute pancreatitis.

is associated with new organ dysfunction/failure. APP = mean arterial pressure - IAP[10]. Ke *et al*[11] found IAP was superior to APP as early marker of evolution and predicting complications of AP.

Table 1 summarizes all the studies evaluating the role of IAP in AP[3,12-26]. None of the studies ever enrolled more than 100 patients. Though results from initial studies were luminary for studies to come yet they suffered from drawback of having unselected patients and non-standardized methodology of measuring IAP and defining IAH/ACS. However a general trend towards uniformity of nomenclature could be seen in studies done from 2009 onwards. However in 2012 major changes were proposed in classification of AP and traditional classification of pancreatitis into mild and severe was further widened to include three or four categories[27,28]. Table 2 contrasts the difference in older Atlanta and recent revised Atlanta and determinant based classification of AP while Table 3 details the modified Marshall scoring system that is used in latest classifications to define organ failure[29]. This further

complicates meaningful synthesis of information from previous studies to present day context where stage down migration of many cases of severe pancreatitis would occur (many cases classified as severe in older classification may now get classified as moderate).

In light of all above arguments and historical perspective it is very difficult to give an accurate estimate of incidence of IAH/ACS that a clinician using modern classification system of AP is likely to face. However deductive reasoning leads to few obvious conclusions: (1) initial reports of very high incidence of IAH/ACS in patients with SAP needs to be considered with view of selection bias; (2) severe disease in older classification system was a more heterogeneous group (included many cases which would now be classified as moderate) and thus point estimates of IAH/ACS in patients classified as "severe" according to present day classification systems are likely to be higher than the low estimates which later investigators have reported; and (3) the observed incidence of IAH/ACS can further vary due to referral bias of worse cases to tertiary care

Table 2 Comparison of Atlanta, revised Atlanta and determinant based classification system of acute pancreatitis

	Atlanta[7]	Revised atlanta[27]	Determinant based system[28]
Mild	Minimal organ dysfunction and an uneventful recovery; lacks the features of severe acute pancreatitis. Usually normal enhancement of pancreatic parenchyma on contrast-enhanced computed tomography	No organ failure No local or systemic complications	No (peri)pancreatic necrosis and no organ failure[2]
Moderate		Organ failure[2] that resolves within 48 h (transient organ failure) and/or local or systemic complications without persistent organ failure	Sterile (peri)pancreatic necrosis and/or transient organ failure (< 48 h)[2]
Severe	Associated with organ failure[1] and/or local complications such as acute fluid collections, necrosis, abscess or pseudocyst	Persistent organ failure[2] (> 48 h) Single organ failure Multiple organ failure	Infected (peri)pancreatic necrosis or persistent organ failure (> 48 h)[2]
Critical			Infected (peri)pancreatic necrosis and persistent organ failure (> 48 h)[2]

[1]Organ failure and systemic complications defined as - Shock (Systolic blood pressure < 90 mmHg), Pulmonary insufficiency (PaO₂ $\leqslant$ 60 mmHg), Renal failure (Creatinine $\geqslant$ 177 μmol/L or $\leqslant$ 2 mg/dL after rehydration), Gastrointestinal bleeding (500 mL in 24 h), Disseminated intravascular coagulation (Platelets $\leqslant$ 100000/mm, fibrinogen < 1.0 g/L and fibrin-split products > 80 μg/L), and Severe metabolic disturbances (Calcium $\leqslant$ 1.87 mmol/L or $\leqslant$ 7.5 mg/dL); [2]Organ failure defined by modified Marshall scoring (Table 3)[29].

Table 3 Modified Marshall scoring system for organ dysfunction[29]

Organ System	Score				
	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	> 400	301-400	201-300	101-200	$\leqslant$ 101
Renal[1]					
(serum creatinine, mmol/L)	$\leqslant$ 134	134-169	170-310	311-439	> 439
(serum creatinine, mg/dL)	< 1.4	1.4-1.8	1.9-3.6	3.6-4.9	> 4.9
Cardiovascular (systolic blood pressure, mmHg)[2]	> 90	< 90 and fluid responsive	< 90 and not fluid responsive	< 90, pH < 7.3	< 90, pH < 7.2

[1]A score for patients with pre-existing chronic renal failure depends on the extent of further deterioration of baseline renal function. No formal correction exists for a baseline serum creatinine $\geqslant$ 134 μmol/L or $\geqslant$ 1.4 mg/dL; [2]Off inotropic support. For non-ventilated patients, the FiO₂ can be estimated from below: (1) Supplemental oxygen (L/min) is room air, the percentage of FiO₂ is 21%; (2) Supplemental oxygen is 2 L/min, 4 L/min, FiO₂ is 25%, 30%, respectively; (3) Supplemental oxygen is 6-8 L/min, FiO₂ is 40%; and (4) Supplemental oxygen is 9-10 L/min, FiO₂ is 50%. A score of 2 or more in any system defines the presence of organ failure.

institutions.

We find data from studies done by Aitken *et al*[26], Bhandari *et al*[25], Bezmarevic *et al*[22] and Dambrauskas *et al*[19] to be useful in this regard as they reported IAP data on all patients with diagnosis of AP visiting their tertiary referral centers. IAH can be expected in at least 17% of patients presenting with diagnosis of AP to a typical tertiary care hospital. Clinicians can expect at least 50% patients with SAP to have IAH. ACS can be expected in at least 15% patients with SAP. No confident estimate can be given for expected incidence of IAH/ACS in patients with moderately severe AP. Similar conclusions have been drawn by other reviewers[30,31].

Pathophysiology and clinical correlates of IAH/ACS in AP

In past decade the central role of zymogen activation due to different reasons as a cause of pancreatic injury has been challenged and modern view accepts both zymogen activation and NF-κB (natural factor kappa beta) activation as parallel players capable of pancreatic injury with aberrant intracellular calcium signaling as the final common pathway[32]. While these mechanisms are playing themselves out in pancreatic acinar cells; the ductal cells may also join the process and enhanced ductal secretions may help wash out the toxins[33]. But they can become overwhelmed and then further contribute to the damage process along with bile. What essentially then ensues is an inflammatory cascade that can propagate to become full blown systemic inflammatory response syndrome (SIRS); which can even lead to multiple organ dysfunction syndrome (MODS) as not only pancreatic acinar cells but inflammatory cells from diverse organs (such as Kupffer cells, peritoneal and alveolar macrophages) become activated during different phases[34]. Peripancreatic adipose tissue upon inflammation can also produce mediators which can facilitate development of SIRS and it can be a more important factor than even waist circumference or BMI in predicting development of SAP[35,36]. There may also be an element of neural mediated inflammation in scheme of events[37]. Initial SIRS is followed by Counter Inflammatory Response Syndrome (CARS) which can contribute to severity

Table 4 Ways in which intra-abdominal hypertension/abdominal compartment syndrome can be predisposed in patients with acute pancreatitis

Diminished abdominal wall compliance
  Prone positioning, head of bed > 30°
  High body mass index, central obesity
  Acute respiratory failure, especially with elevated intrathoracic pressure
  Edema due to excess fluid administered during resuscitation
Increased intra-luminal contents
  Gastroparesis
  Ileus
  Colonic pseudo-obstruction
Increased abdominal contents
  Ascites (due to causes such as acute fluid collections, liver dysfunction)
Capillary leak / fluid resuscitation (overload)
  Acidosis (pH < 7.2)
  Hypotension
  Hypothermia (core temperature < 33 ℃)
  Coagulopathy (platelets < 55000/mm^3 or prothrombin time > 15 s
or partial thromboplastin time > 2 times normal or international
standardised ratio > 1.5)
  Massive fluid resuscitation (> 5 L/d)
  Oliguria
  Sepsis

as much as protease activation[38]. CARS leads to suppression of immune system and can facilitate complications such as infection of sterile pancreatic necrosis and nosocomial infections. Certain iatrogenic factors such as timing of resuscitation, quantity of administered fluids and enteric nutrition also modulate this disease process although they are incompletely understood at present[39,40].

Traditional view of gut has been that of an innocent bystander suffering collateral damage but increasingly it is being understood that it (along with abdomen) further contributes in two major inter related ways in the ongoing scheme of events by means of (1) gut barrier dysfunction; and (2) IAH/ACS[41,42]. Gut barrier dysfunction implies damage to intestinal epithelial cells and tight junctions leading to increased intestinal permeability, and pooled meta analyses determined prevalence has been determined to be 59% (95%CI: 48%-70%). It occurs due to ischemia reperfusion injury to gut due to reflex splanchnic vasoconstriction in initial phase which later gets overcome by resuscitation. Resultant increased toxin and enteric bacterial translocation to portal circulation and mesenteric lymph nodes can lead to SIRS, secondary infection, MODS and ultimately death[43,44]. IAH/ACS also contributes to gut barrier dysfunction[42,45].

Further, all studies on IAH/ACS in AP have found it to be variably associated with increased complications and severity of disease (variably in form of higher incidence of organ failure, need for Ⅳ fluids/inotropic support, pancreatic necrosis, extent of pancreatic necrosis, infected pancreatic necrosis, morbidity, hospital stay, and ultimately mortality). There are multiple ways in which IAH/ACS is predisposed in AP (Table 4)[10]. In fact IAH/ACS can contribute to dysfunction in almost

any organ[46]. Increased IAP reduces cardiac function with reduced return from Inferior and superior vena cava as well as portal vein while increasing peripheral vascular resistance. It leads to splinting of diaphragm with resultant increased airway pressures and reduced pulmonary capacity; hypercapnia, acidosis and hypoxia can ensue. The splanchnic, mesenteric and hepatic perfusion pressures also decrease which can lead to gut barrier dysfunction as mentioned before as well as hepatic dysfunction potentiating coagulopathy and worsening acidosis. Changes due to abdomino thoracic pressure transmission have been even noted in organs such as orbit and cranium. Renal perfusion pressure decreases due to direct compression effect on renal arteries, veins and kidney parenchyma as well as reduced cardiac output; oliguria and anuria can set in with increasing pressures with simultaneous activation of renin angiotensin system[47]. Indeed, oliguria is one of the early hallmark sign of increased IAP. Recognition of such widespread changes lead WSACS to recognize term "polycompartmental syndrome" ("where two or more anatomical compartments have elevated compartmental pressures") in 2013 consensus definitions[10]. Moreover increases in IAP have been found to positively correlate with reduced transmucosal gastric pH and increased levels of IL-1β, IL-6, TNFα and C-reactive protein in animal models while in human surgical intensive care (ICU) patients it has been found to correlate with IL-10 and adenosine[42,48]. Bodnár *et al*[49] proposes central role of adenosine (released from hypoxemic tissues) in cyclical events of ACS where adenosine induced splanchnic vasodilatation increases IAP and also causes renal arterial dysfunction. Renal dysfunction plays important role propagating other organ dysfunction. They thus propose monitoring adenosine and/or IL-10 in monitoring progression of ACS and results of therapeutic interventions. On a parallel stream of thought pancreatic inflammation is thought to trigger innate immune system which subsequently triggers adaptive immune system. Previously researchers found reduced levels of CD4$^+$ cells in patients with severe disease which also correlated with increased incidence of complications[50,51]. However recently Liu *et al*[52] while revisiting the same concept in SAP found that proportions of CD4$^+$ were significantly lower in patients with ACS in comparison to those with IAH. They further found a CD4$^+$ T cell proportion of 30.3% on day 1 predicted ACS with an area under curve of 0.774, with sensitivity and specificity of 82.5% and 72% respectively.

It is thus easy to understand why IAH/ACS should be considered as a spectrum in continuum, and how it is difficult to discriminate changes due to SIRS of AP from those due to IAH/ACS[31]. But ACS has immediate critical effects on multiple organ systems due to additional physico-mechanical effects which are associated with very high mortality (if left untreated). It may not be unreasonable to argue that few cases of early mortality in AP may be due to untreated ACS[53].

ACS: Epiphenomenon or not? - Are we missing the focus?

Concern is expressed whether IAH/ACS is an epiphenomenon or a driver of events in AP as it has direct bearing on utility of its surveillance and management, and little would be gained if ACS only developed as a terminal phenomenon to a series of morbid events[30,54]. Indeed, almost all clinicians come across critically ill patients with multiple organ dysfunction who have almost all predisposing factors for development of IAH/ACS and little hope for any survival. We cannot reasonably compare clinical picture of acute disease process of pancreatitis with those of chronic and terminally ill patients. Moreover, understanding of pathophysiology from discussed previous evidence proves beyond doubt that ACS is not a silent spectator; so whether IAH/ACS develops as an epiphenomenon or not, it "definitely contributes negatively" to the scheme of events. Two additional points merit attention - almost all studies on IAP in AP conclude that IAH/ACS develops early in the disease course (usually present at admission or within first 2 d). Thus whether IAH/ACS is an epiphenomenon or not can only be judged by carefully timed measurements of IAP before organ failure manifests. Which brings us to the second point of findings in a recent observational study of natural history of IAH in AP where Aitken *et al*[26] found development of IAH/ACS to be sentinel event before progressive organ failure ensued in several patients (an experience with which we also agree). To this we may add that it is practically impossible to detect IAP in a patient prior to when he presents to the hospital; thus natural history of IAP in patients who present with manifest IAH to hospital will remain elusive. Only circumstantial human evidence and experience from animal studies can be used to draw conclusions. A recent animal study by Li *et al*[45] supports the "driver role" of IAH/ACS where they propose early mitigation of IAP as an approach to treat acute necrotizing pancreatitis and hint towards a 6 hour window where appropriately diverted efforts may deliver results. AP was induced in Sprague-Dawley rats and it was observed that IAP showed a continuous upward trend with time with peak in rising rate at 6 h; after which rapid clinical deterioration occurred. Moreover, TNF-α (inflammatory marker), diamine oxidase and D-lactate (markers of gut barrier dysfunction) also peaked at the same time as IAP. When we consider all these arguments in conjunction with evidence of IAH/ACS being associated with higher incidence of complications such pancreatic necrosis, extent of necrosis, presence of infected necrosis, hospital stay and mortality then clinical reasoning only directs attention to surveillance of IAP in appropriate patients and additional efforts to determine optimum management strategies to tackle it.

We find it interesting that the first publication suggesting unique intervention towards ACS in early phase of SAP came from United States in 2002, but latest clinical guidelines (2013) yet do not acknowledge possible unique role of IAP[9,55,56]. We agree that guidelines have to rely on higher order evidence but we believe sufficient evidence exists to merit at least surveillance of IAP in selected subgroup of patients with AP. On an encouraging note Japanese Society Hepato-Biliary-Pancreatic Surgery have been the first to acknowledge the importance of ACS in evolution of AP and recommend sequential measurement of IAP for cases with excessive fluid infusion, high severity, renal and respiratory complications, and fluid accumulation in multiple areas as observed by computed tomography (CT), in recognition of fact that presence of ACS may increase mortality[5]. Lack of support for IAP surveillance from major guidelines is not without consequences and it could be one factor potentiating lack of awareness of IAH/ACS among clinicians treating AP as results from a recent clinical survey indicate less than 30% clinicians being aware of correct definitions of IAH/ACS[57]. It also precluded us from including decompressive laparotomy for ACS in early SAP in our hospital disease management policy in 2009 as regulatory requirements mandated hospital policy to be based on latest accepted national or international clinical guidelines (though we offered it on individual basis with consent and discussion of best available literature)[26]. Such situation may also be faced by other clinicians. This also acts as a barrier to gathering data on the next obvious vexing question.

Does surveillance and intervention for IAH/ACS reduce mortality?

It makes straightforward clinical argument that - "if animal studies and human data show a time period where IAH/ACS occurs before manifest organ failure; and if that time period is of sufficient duration to allow reasonable attempts to correct IAH/ACS; or if IAH/ACS are proximate driver of events which lead to clinical deterioration; implying that they may not be terminal events which occur at the end of morbid clinical incidents" - then, surveillance and intervention for IAH/ACS should be proven to reduce mortality.

The first report in 2002 on abdominal decompression in three patients for ACS in SAP reported one survival[9]. But managing all three patients convinced the authors to recommend consideration for decompressive laparotomy in early phase of SAP; much radical suggestion in contrast to dominant recommendation for conservative management in early phase of disease. A year later, Tao *et al*[58] reported their experience from China where 15 out of 18 patients receiving decompressive laparotomy for ACS survived while 4 out of 5 patients managed conservatively died, and they recommended early diagnosis of ACS for optimum management. On the contrary, in 2005 De Waele *et al*[12] reported universal mortality following decompressive laparotomy for ACS in four patients and cautioned against its routine use. Subsequently a large study by Chen *et al*[17] in 2008 demonstrated obvious amelioration in clinical variables within 24 h after decompression for ACS in patients with SAP and 25% patients survived. They recommended

a low threshold for intervention in patients with AP determined by presence of IAH and early signs of changes in physiologic variables. Further, retrospective study in 26 consecutive cases of decompressive laparotomy for ACS in SAP by Mentula *et al*[20] in 2010 showed 46% mortality (decompressive laparotomy improved renal and respiratory function) which came down to 18% when surgical decompression was carried out within first four days after disease onset. This prompted them to conclude that early decompression reduced mortality. In 2011 Leppäniemi *et al*[59] reported survival in 6 out of 10 patients with a novel minimally invasive endoscopic method of subcutaneous linea alba fasciotomy for decompression of ACS in SAP. However, again in 2012 Bezmarevic *et al*[22] reported mortality in 3 out of 4 patients who underwent decompression of ACS in various time points in disease course; though one patient who did not undergo decompressive laparotomy also did not survive. On the contrary, more recently Boone *et al*[23] in 2013 reported survival in 6 out of 12 consecutive cases with decompressive laparotomy for ACS in SAP with improvement in clinical parameters of multiple organ systems in most cases. In the same year Davis *et al*[24] also reported encouraging results of decompressive laparotomy with survival in 13 out of 16 patients with ACS with no difference in survival whether patients were morbidly obese or not. This stands in stark contrast to prospective observational studies by Bhandari *et al*[25] and Aitken *et al*[26] where all patients with ACS died with conservative approach (avoiding decompressive laparotomy). Recently Jacob *et al*[60] reported their experience from central Australia with early surgical intervention in AP for twin indications of early infected pancreatic necrosis and ACS (not controlled with medical management) over period of 8 years (2005-2012) and reported 0% mortality for SAP in 114 patients.

Could the survival data from decompressive laparotomy for ACS be away from real achievable optimum?

Recognition of clinical heterogeneity of severe pancreatitis and importance of organ failure is one of major advances in our understanding of pancreatitis in the past decade and latest modifications in classification systems of pancreatitis reflect those (apart from better defining complications of AP)[27,28]. Similar paradigms become apparent in ACS: (1) ACS by definition requires development of organ failure but then it further worsens it and induces organ failure in new organs; (2) there may be a reasonable time period between onset of ACS and then further onset of organ failure; (3) there may be heterogeneity in reported outcomes of intervention in ACS because of differences in timing of intervention, as multi organ failure can be irreversible after a point; and (4) there may be other non-modifiable or modifiable but with serious demands on human physiology factors (such as comorbidities, old age) which independently adversely impact survival. All these arguments taken together coherently explain 0% as well as 100%

mortality for intervention in ACS. Indeed, almost all the authors reporting outcomes of decompressive laparotomy in ACS except De Waele *et al*[12] and Bezmarevic *et al*[22] recommended early rather than late intervention. These hints towards greater likelihood of better survival than what eyeballing combined results of these studies would indicate. A recent meta analyses on ACS in AP (103 patients) concluded with 49% mortality in patients with ACS (with morbidity upto 90%) *vs* 11% mortality in those without ACS when 84% patients underwent invasive intervention for ACS (which was decompressive laparotomy in majority)[61]. The authors similarly acknowledged that optimum timing and method of intervention for ACS could impact outcomes and recommended further evaluation. In support of human data, animal experiments in controlled environment show coherent conclusive proof that well timed surgical decompression for ACS in SAP reduces mortality compared to delayed decompression[62]. Ke *et al*[62] divided 32 porcine animal models of SAP lasting 24 h into 4 equal groups and induced ACS in three groups. Surgical decompression was carried out in ACS groups at 6, 9 and 12 h respectively and effect on survival was seen. The survival time progressively increased with increasing promptness of timing of decompression and animals in 6-h group had survival times similar to those with SAP without ACS. On a parallel stream of thought Orlando Regional Medical Center (United States) in 2010 reported first large scale prospective clinical data where use of continually revised IAH/ACS management algorithm showed improvement in survival in trauma victims from 50% to 72% in ICU setting in a Level 1 trauma center[63]. Unsurprisingly, with time De Waele *et al*[64,65] changed their position (from exercising caution in recommending decompressive laparotomy) as early as 2008, and now recommend to identify patients early for IAH/ACS during course of disease, and not to hesitate to offer decompressive laparotomy in case non operative methods seem to not help in AP.

Could doing surveillance for IAH/ACS be useful in other ways too?

IAH/ACS is attractive for purpose of prognosis and marker of disease severity for three reasons: (1) It develops early during course of disease; (2) It has been noted to be a proximate event prior to clinical worsening; and (3) It is associated with worse outcomes (may even have a causal role as its coherent fit in clinical events of disease progression and pathophysiology suggests). Unsurprisingly it compares favorably to commonly used markers of disease severity. The pioneering paper with Pupelis *et al*[3] concluded with the final words "Marked increase of the IAP should be considered a serious prognostic sign in patients with severe AP" as they found zero mortality in patients who did not develop IAP > 25 cm H_2O during disease course *vs* 36% mortality in those who did. Subsequently authors reported IAH/ACS to be associated with higher Ranson score[12,17], APACHE 2 score[12-19,24-26], CT severity index[16,25],

Marshall score[17,18,25], Glasgow-Imrie score[19,24,26], SOFA score[13,14,18], Lung injury score[18], multiple organ dysfunction score[19], infected pancreatic necrosis[16,17,25], procalcitonin levels[22], C Reactive Protein levels[22,26], maximal creatinine[14], maximum base deficit[14], lower serum calcium levels[21], lower platelet counts[13], requirement for vasoactive drugs[16], lower enterally provided volume[13], requirement for total parenteral nutrition[16], operative intervention[16,21], and length of ICU stay[12,14,18,21,25]. Definition of ACS by itself implies presence of organ failure and most studies universally conclude ACS to be associated with higher mortality as discussed previously. In fact it compares similarly in terms of sensitivity/specificity for predicting SAP when compared to APACHE 2 Score[25,26], Glasgow Imrie score[26], C reactive protein[26] and procalcitonin levels[22]. Bodnár *et al*[42] recommend presence of IAH/ACS to be a criteria for referral to higher center (a recommendation to which we agree)[25].

Could IAP be a confounder and contribute to heterogeneity in common management related issues in AP?

Confounder is an unobserved exposure that is associated with exposure of interest and is a potential cause for outcome of interest. Failure to control it damages the internal validity of experiment. Similar serious issues occur when population studied under controlled experiment is heterogeneous. The present American College of Gastroenterology as well International Association of Pancreatology/American Pancreatic Association guidelines (which are essentially based on evidence gathered by meta analyses) highlight conflicting evidence on three important areas in management of AP: (1) fluid resuscitation; (2) nutrition; and (3) antibiotics[55,56]. IAH/ACS offers explanation as area of potential heterogeneity as well as confounding, which can coherently align observed outcomes in prevalent pathophysiologic paradigm. This could potentially help plan better individualized treatment for patients with more severe spectrum of disease.

Fluid resuscitation

It is an easy to understand hypothesis that pancreatic hypoperfusion in AP would be worsened by hypotension and experiments in rat models confirm the same[66]. But translational outcome of this evidence falters in humans and contrarily few recent studies indicate better outcomes with non-aggressive fluid resuscitation protocols[67,68]. In fact a recent systematic review concluded with "equipoise" over the question of non-aggressive, *vs* aggressive, *vs* goal directed fluid resuscitation protocol for AP[69]. Most experienced clinicians treating AP would agree that fluid resuscitation is not much problematic with mild AP, and they do not need aggressive fluid management; while also at the same time understanding that that too little fluid is also obviously harmful in AP. We now also better understand that severe pancreatitis according to old Atlanta classification was in fact a heterogeneous group and present classification has set the bar higher for severe disease. This can partially explain incoherent results from previous studies where study cohorts may have included an unrecognized proportion of patients with not as much worse disease but still labelled as severe. We now understand from pathophysiology of ACS that fluid therapy can be tricky, because aggressive fluid therapy may worsen IAH/ACS due to capillary leak and increasing abdominal organ and parietal wall edema while reducing abdominal perfusion pressure; which can have deleterious effects on multiple organs including reduced cardiac index. Thus, it is obvious to see ACS as a confounder here because it may be associated with both aggressive fluid resuscitation as well as poor outcomes. Moreover ACS also adds to clinical heterogeneity among patients with moderate/severe AP. IAH/ACS also adds to confounding in resuscitation protocols which rely on measurement of central venous pressure (CVP) as a goal (used in goal directed fluid therapy protocols derived from sepsis guidelines) as it has been shown that IAP has a "inverted U shaped" relationship with CVP with peak around 15 mmHg[70,71]. This has important therapeutic implications as CVP decreases beyond this point and same CVP value may be attained in two patients with entirely different fluid requirements due to different IAP. Similarly ACS will predispose to reduced urine output due to direct effect on kidneys and thus protocols which rely on urine output have a potential for confounding by IAP. In general, correction factors with regards to IAP have been proposed for CVP (IAP may lead to falsely high CVP due to abdomino thoracic transmission), and usually patients with higher IAP have lower effective circulatory volumes with higher third space losses[46]. Thus initially they paradoxically need more fluids (with close monitoring of IAP) while later if higher grades of IAP/ACS manifests (due to multiple reasons; possibly also including too much fluids if not judiciously administered previously) then immediate measures to reduce IAP (draining excess third space fluid accumulations, decompressing bowel, improving abdominal wall compliance, *etc.*) are required along with possibly more judicious fluid management protocol[72]. Though crystalloids remain the most common used resuscitation fluid, Zhao *et al*[73] report using combinations of crystalloids and colloids (hydroxyl ethyl starch and glutamine) to result in lower incidence of renal dysfunction, MODS and ACS when compared to resuscitation with normal saline alone. However mortality was not different between groups. It is also imperative to understand that renal dysfunction and attendant fluid imbalance due to direct effects of manifest ACS can't usually be reversed by any modification of fluid management protocol and goals of directed therapy would have to consider management of ACS to remain meaningful. Clearly combined hemodynamic and fluid specific indices are better methods to determine fluid requirements and further research with elimination of confounding and heterogeneity is required

to better answer this conundrum.

Nutrition

Enteric feeding is proposed to prevent bacterial overgrowth and reduce bacterial translocation and is one of the ways shown to reduce mortality among patients with AP[74]. Timing of initiation of enteric feeding is critical and benefits seem to be lost if it's delayed beyond 48 h. Although exact patho-physiologic mechanism is unknown but certain issues are highlighted: (1) enteric feeds may increase gut motility due to osmotic effect and thus reduce ileus which may also prevent overgrowth of bacteria and change in micro flora in stagnant bowel; (2) it may prevent gut atrophy (as intestinal epithelial cells may derive direct nutrition from luminal contents) and thus decrease bacterial translocation; and (3) timing of initiation of nutrition may be important as infectious complications can occur very early in AP and current paradigm proposes gut as a source of culprit bacteria. It is easy to see how IAH/ACS fits into above scheme (promotes gut barrier dysfunction and bacterial translocation) and can contribute as a confounder as it may delay initiation of enteric feeds, as patients with IAH/ACS are usually intolerant to it and it may be inadvisable to force feed patients with feeding intolerance[75]. Moreover ACS may itself have been caused by ileus necessitating bowel drainage. Yet it is attractive to align to concept of low volume constant enteric feeds (in comparison to large volume cyclical feeds) in patients with ileus to improve tolerance, thus retaining benefits of enteric nutrition; a concept also endorsed by the American Society for Parenteral and Enteral Nutrition[76,77]. The same concept also coherently aligns with those with rising IAP where low volume constant enteric feeds may theoretically reduce ileus (by promoting gut motility) and prevent IAH (thus promoting splanchnic flow and further aiding gut function). Thus understanding of IAH/ACS explains why initiating early enteric feeds may not necessarily increase IAP in every case, moreover it can be of benefit to those with IAP less than 15 mmHg (even preventing development of IAH), and it may not be appropriate in few cases with manifest ACS who may be intolerant to food where delicate balance of low volume constant enteric feeds/judicious use of parenteral nutrition (in first three days, and as there is no indication for fasting) with early return to enteric feeds may have a place[75]. Thus future trials on enteric nutrition should account for heterogeneity as well as confounding by IAH/ACS.

Antibiotics

There is conflicting data on prophylactic antibiotic use in AP but meta analyses conclude that there is no evidence of benefit from "routine" use[78]. However sample size of RCTs have been rather small and trends (though non-significant) show improvement in mortality and incidence of infections. Clinical heterogeneity reconciles some differences in non-intuitive results of meta analyses since we now understand that severe pancreatitis as defined in older Atlanta classification was not a homogenous entity and included some patients with milder forms of disease with low risk for infections and mortality. Understanding pathophysiology of IAH/ACS further opens up the debate as gut barrier dysfunction and bacterial translocation are inherently explained, and it further contributes to heterogeneity even by present classification system. Overall it's easier to understand with current paradigms (including concepts of IAH/ACS) why "lack of benefit or presence of harm" of prophylactic antibiotics is yet to be proven, and this is not in variance with understanding that infection of pancreatic necrosis may occur much earlier than when it clinically manifests[79]. Since detection of infected pancreatic necrosis can be difficult, and since manifestations of ACS (with inherent organ failure as pre-ordained by definition) are indistinguishable from severe sepsis (and even septic shock), and since there is evidence of harm from delay in instituting antibiotics; position paper by Mentula *et al*[72] for management of IAH/ACS in AP recommend selective prophylactic antibiotic use in patients with organ dysfunction, IAH and other predictors of severe disease till organ dysfunction resolves and there is no evidence of infection. Since IAH/ACS is associated with increased incidence of infected pancreatic necrosis and mortality independently, it should be considered as a contributor to heterogeneity as well as confounding in future studies, and be appropriately analyzed before recommendations are made[16,17,25].

DISCUSSION

The aim of this review was to generate debate on role of IAP and how it may contribute to lowering internal validity in much of available evidence with potential to further individualize treatments to more homogeneous subgroups of patients with AP (a desired goal of management guidelines). Comprehensive coverage of management strategies of IAH/ACS are beyond the scope of this review but are covered well elsewhere[10]. We do not recommend universal IAP surveillance as there is no evidence of advantage of IAP surveillance in patients with milder forms of disease[19,25,80]. But we believe that sufficient evidence exists to selectively offer surveillance for IAH/ACS in a subgroup of patients with AP. We agree with recommendations of Japanese Society Hepato-Biliary-Pancreatic Surgery to recommend IAP surveillance in patients with excessive fluid infusion, high severity, renal and respiratory complications, and fluid accumulation in multiple areas as observed by CT[5]. The current guidelines by WSACS on diagnosis and management of IAH/ACS are also a reference point and offer a roadmap for practicing clinician[10]. SAP is a disease whose management requires close coordination of gastroenterologists, surgeons, intensivists, nursing staff and allied health professionals. Managing open abdomen due to any cause is indeed no small task; but management of open abdomen following surgical intervention has undergone significant changes in past decade.

With newer concepts of early closure, prevention of loss of abdominal domain and negative pressure wound therapy; data on morbidity and mortality following decompressive laparotomy for ACS may stand further revised[81]. Although we have discussed evidence with relevance to AP; much reliably similar and consistent evidence for role and management for IAH can be gleaned from diverse fields of trauma care, burns, sepsis and pediatrics[65]. Overall there is much to expect from upcoming 10 years where we expect to revisit old conclusions in new light of greater homogeneity and less confounding as ACS in AP is a unique entity and incorporating surveillance for IAP in AP offers potential window to further refine diagnostic groups of patients. In the least we expect that IAP be given its due place in future practice guidelines and that recommendations be formed with help of a broader panel with inclusion of clinicians experienced in management of IAH.

CONCLUSION

IAH can be expected in at least 17% of patients presenting with diagnosis of AP to a typical tertiary care hospital. Clinicians can expect at least 50% patients with SAP to have IAH. ACS can be expected in at least 15% patients with SAP. There is increasing data to show that surveillance and management strategies specific to IAH/ACS increases survival in AP. IAH/ACS is useful as a predictive marker for severe disease and prognostic marker for inferior outcomes. Understanding concepts of IAP may help resolve inconsistencies in available literature for management of AP especially in areas relating to fluid management, antibiotic prophylaxis and nutritional management and as such represents an advance in understanding. Future clinical guidelines on AP must include recommendations for surveillance and management of IAH/ACS.

COMMENTS

Background
Towards the end of last decade clinicians increasingly realized the heterogeneity in broad classification of acute pancreatitis (AP) into mild and severe groups and thus recently classification systems were broadened to include more groups. This was one important factor which lowered internal validity of clinical research as patients with intermediate severity disease confounded results from both mild and severe disease groups. Unsurprisingly meta analyses concluded with equipoise on important issues such as antibiotic prophylaxis or fluid resuscitation. Meanwhile increasing evidence has started accumulating about intra-abdominal pressure (IAP) as an important point of specific intervention in AP with potential to reduce mortality.

Research frontiers
The exact epidemiology of IAP remains to be established in new context of new classification systems of AP, but intra-abdominal hypertension (IAH) can be expected in at least 50% patients with severe AP with 15% expected to qualify for intervention specific for abdominal compartment syndrome (ACS). This poses a potential for further refining even recently proposed classification systems as increasing research points towards ACS as a key factor explaining confounding as well as heterogeneity in disease management related issues. ACS (which should be understood as a continuing spectrum of IAH) contributes actively towards multiple organ dysfunction independent of initiating cause

and evidence indicates decreased mortality when it is specifically addressed. It complicates issues related to antibiotic prophylaxis, nutritional and fluid management as such patients require intensive individualized management and routine management guidelines do not address its pathophysiology.

Innovations and breakthroughs
This paper is an up to date summary of available evidence about IAP and AP with specific focus on how understanding pathophysiology of IAP helps coherently explain gaps in existing management related issues of AP and why present evidence in AP concludes with equipoise on important aspects. It unambiguously concludes with broad suggestion to include surveillance for IAP in future management related guidelines for AP.

Applications
ACS in AP is a unique entity and incorporating surveillance for IAP in AP offers potential window to further refine diagnostic groups of patients. Precise answers to clinical questions can be obtained if study populations are homogenous and free from confounding potentially aiding future research to conclude with more unambiguous conclusions.

Terminology
IAP is global pressure inside the abdominal cavity and measured preferably by transvesical method, with maximal instillation of 25 cc saline, in supine position, measured at end expiration, with zeroing done at the level of mid axillary line; IAH - defined by a sustained or repeated pathologic elevation of IAP $\geqslant$ 12 mmHg with grading as follows: Grade Ⅰ: IAP 12-15 mmHg, Grade Ⅱ: IAP 16-20 mmHg, Grade Ⅲ: IAP 21-25 mmHg, Grade Ⅳ: IAP > 25 mmHg; ACS - defined as a sustained IAP > 20 mmHg [with or without an abdominal perfusion pressure (APP) < 60 mmHg] that is associated with new organ dysfunction/failure; APP - mean arterial pressure - IAP.

Peer-review
The authors perform an extensive review on the current literature which they provide as evidence for their conclusion. This is an attractive and relevant paper.

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