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Antibiotic use in acute pancreatitis: an audit of current practice in a tertiary centre.

Running title: Antibiotics in acute pancreatitis.

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Abbreviations: sd: standard deviation. 95% CI: 95% confidence interval. GI: gastrointestinal.

Abstract

Introduction

Intravenous antibiotic prophylaxis is not recommended in acute pancreatitis. According to current international guidelines antibiotics together with further intervention should be considered in the setting of infected necrosis. Appropriate antibiotic therapy particularly avoiding over-prescription is important. This study examines antibiotic use in acute pancreatitis in a tertiary centre using the current IAP/APA guidelines for reference.

Methods

Data were collected on a consecutive series of patients admitted with acute pancreatitis over a 12 month period. Data were dichotomized by patients admitted directly to the centre and tertiary transfers. Information was collected on clinical course with specific reference to antibiotic use, episode severity, intervention and outcome.

Results

111 consecutive episodes of acute pancreatitis constitute the reported population. 31 (28%) were tertiary transfers. Overall 65 (58.5%) patients received antibiotics. Significantly more tertiary transfer patients received antibiotics. Mean person-days of antibiotic use was 23.9 (sd 29.7) days in the overall study group but there was significantly more use in the tertiary transfer group as compared to patients having their index admission to the centre (40.9 sd 37.1 vs 10.2 sd 8.9; $P<0.005$). Thirty four (44%) of patients with clinically mild acute pancreatitis received antibiotics

Conclusions

There is substantial use of antibiotics in acute pancreatitis, in particular in patients with severe disease. Over-use is seen in mild acute pancreatitis. Better consideration must be given to identification of

prophylaxis or therapy as indication. In relation to repeated courses of antibiotics in severe disease there must be clear indications for use.

[abstract word count: 245].

Introduction

Infection of pancreatic necrosis is the most frequent cause of late mortality in severe acute pancreatitis [1-3]. Antibiotic prophylaxis to reduce infective complications in acute pancreatitis was evaluated in a series of randomized trials [4-12]. However meta-analyses of these trials do not support antibiotic prophylaxis in acute pancreatitis [13-15]. Summarising this evidence, the International Association of Pancreatology/American Pancreatic Association (IAP/APA) produced evidence-based guidelines in 2013 for the management of acute pancreatitis. These state that intravenous antibiotic prophylaxis is not recommended for the prevention of infective complications in acute pancreatitis. The guidelines support antibiotic use in "case of suspected infection of necrotizing pancreatitis" together with consideration for further intervention [16].

Given the dearth of specific, effective interventions in acute pancreatitis, optimal use of antibiotics is important. Under-use may lead to inadequate treatment of infection whereas over-use encourages emergence of resistant bacterial flora and leads to a reduction in available treatments if and when infection does occur. In clinical practice it is likely that the reasons underlying antibiotic use and mis-use in acute pancreatitis are complex and multi-factorial. Arguably, the most frequent confounding factor is that making a distinction between infection and the systemic inflammatory response of pancreatitis at the bedside can be difficult. Clinical signs such as fever and tachycardia may be similar and both scenarios are associated with an elevated leukocyte count and C-reactive protein. Further, infection and systemic inflammation can co-exist. Poor compliance with guidelines for antibiotic use in acute pancreatitis is a genuine and important clinical problem seen worldwide [17]. In order to better understand antibiotic use in the contemporary management of acute pancreatitis this study takes the form of an overview of management in a tertiary referral specialist hepato-pancreato-biliary (HPB) centre. The study examined antibiotic use in patients admitted directly to the centre and also in tertiary referral patients initially admitted to other hospitals and transferred during the course of their episode of acute pancreatitis. The current IAP/APA guidelines were used as a reference standard.

Methods

Design and setting

This is a single-centre clinical cohort study based in the regional specialist HPB service of the Manchester Royal Infirmary (MRI) which serves a 3.2 million predominantly urban conurbation of the Greater Manchester and Cheshire Cancer Network.

Study period

The inclusion period is the 12 months from 1st October 2014 to 1st October 2015.

Definitions of acute pancreatitis

The diagnosis of acute pancreatitis was confirmed by the presence of (typically) severe epigastric pain accompanied with ≥ 3-fold elevation in serum amylase or by characteristic findings on contrast-enhanced CT scan. Clinical severity of acute pancreatitis (mild, moderate, severe) was assessed according to the revised Atlanta classification (2012), based on the presence of transient organ failure and local or systemic complications [18]. The diagnosis of infected pancreatic necrosis was based on positive culture of drained peripancreatic fluid or gas containing collection on CT.

Data collection

Data were collected prospectively from 1st January 2015 (retrospectively for the preceding three months to complete the 12 month study period) by accessing patient notes and using a bespoke case-report form. All data were collected from time of admission to the tertiary care centre including calculation of Acute Physiology and Chronic Health Evaluation (APACHE II) and Marshall Organ Dysfunction scores (MODS). All patients ≥18 years old admitted with acute pancreatitis were included in the study. Data were collected on demographic profile, days of in-patient stay and setting (in-patient ward, High Dependency unit with non-invasive ventilation or critical care with ventilatory support) whether the index

admission was to this hospital or whether the patient was a tertiary transfer. Re-admitted patients were remained in their originally allocated category (for example an index admission patient who was re-admitted, remained an index admission). Data were collected on aetiology [biliary, alcohol, endoscopic retrograde cholangiopancreatography(ERCP)-induced, drug-induced, traumatic or idiopathic], admission amylase and C-reactive protein.

Antibiotic use

Use of antibiotics was recorded together with number of days of treatment (defined as person-days of antibiotic use). During the period of this study there was published guidance for the tertiary centre relating to antibiotic use based on and complying with the IAP/APA guidelines [16]. To further explore the use of antibiotics in this disease, use was categorised as either for acute pancreatitis (for example severe disease or presence of infected necrosis) or for a secondary condition during in-patient stay such as upper respiratory tract infection.

Use of computed tomography (CT)

Use of CT scan was recorded and Balthazar CT severity score calculated for the purposes of the study [19]. For tertiary transfer patients, the information relating to CT refer to scans undertaken in this centre.

Radiologic, endoscopic and surgical interventions

Fine needle aspiration of pancreatic necrosis was not routinely employed in this unit during the period of this study. A record was made of other radiologic intervention such as percutaneous catheter drainage and also angiographic radiological intervention such as mesenteric angiographic embolization undertaken during index admission. Endoscopic interventions undertaken during the index admission were recorded. Similarly, surgical interventions were recorded. For the purposes of this study, surgical necrosectomy refers to minimally invasive necrosectomy.

Analysis plan

Management of patients admitted for acute pancreatitis was summarised descriptively for study variables, including demographics, disease and management variables, in particular number of days of antibiotic treatment and type of antibiotic used. Use of antibiotics was assessed for compliance with the IAP/APA guideline recommendations and contrasted for index and tertiary transferred patients. The influence of level of antibiotic use and adherence to guidelines upon confirmed infection rates, GI complications and length of stay was explored using appropriate general linear models adjusted for recorded patient, disease and management factors and covariates. Thus a p-value of < 0.05 was considered to indicate statistical significance for findings meriting further investigation without adjustment for multiple comparisons. Bootstrapped estimation was used for continuous variables, analysis of proportions used Fisher's exact test. Analysis was conducted using SPSS v21 (IBM Corp; IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY, USA).

Ethics.

The study was categorised as an audit by the Central Manchester Hospitals Foundation Trust Research and Development office and was registered with the hospital's audit department (audit number 6513).

Results

Demographic profiles

111 consecutive episodes of acute pancreatitis constitute the reported population. Of these, 31 (28%) were initially admitted to other hospitals across the region and subsequently transferred to this centre for tertiary care. The demographic characteristics are seen in Table 1. Ten tertiary referral patients were transferred with a MODS score of 1 or 2. Gallstones were the most frequent cause of acute pancreatitis with alcohol being the second most common cause.

Disease severity

There were significantly more episodes of radiologically and clinically severe acute pancreatitis in the tertiary transfer group. Physiological derangement was worse in transferred patients with haemoglobin and albumin being significantly lower at time of transfer (table 2).

Index admissions compared to tertiary transfer

There was no significant difference in age between those patients admitted directly to the MRI and those admitted as tertiary transfers (55.6 SD 20 vs 54.3 SD 14.7; p = 0.712). Thirty nine (49.4%) of patients having their index admission to the MRI had an MODS score of 0 compared to 18 (64.3%) of tertiary transfers by the time of their arrival (p=0.062). Pancreatitis severity was worse in transfer patients. The index admission MOD scores have a much longer tail of severity than the tertiary variables.

Diagnostic and interventional radiology

CT severity index was significantly worse in patients who were tertiary transfers (7.3 ± 2.8 vs 3.1 ± 2.5; P <0.001). 19 (61.3%) of patients who were tertiary transfers underwent percutaneous catheter drainage compared to 3 (3.7%) who had their index admission to the tertiary centre.

Endoscopic and surgical interventions

Eighteen patients (16.2%) underwent ERCP ± stent. All patients undergoing necrosectomy in this series were admitted with severe acute pancreatitis.

Antibiotic use

Overall 65 (58.5%) patients received antibiotics. Significantly more tertiary transfer patients received antibiotics. Mean person-days of antibiotic use was 23.9 (sd 29.7) days in the overall study group but there were significantly more person days of antibiotic use in the tertiary transfer group as compared to patients having their index admission to the centre (40.9 sd 37.1 vs 10.2 sd 8.9; P<0.005).

Assessed by episode severity (table 3), 34 (44%) of patients with clinically mild acute pancreatitis received antibiotics although in 10 (13%) of these patients, the indication was for infective complications occurring during the inpatient admission with acute pancreatitis (table 3). In contrast, 17 (100%) patients with severe acute pancreatitis received antibiotics. There was a broad range of antibiotics used (table 4) with the combination of amoxicillin and clavulanic acid being the most frequently prescribed (30 patients [27%]). Fourteen patients (12.6%) had two antibiotic regimens, 12 (10.8%) receiving 3 distinct courses of antibiotics and 5 (4.5%) patients receiving four courses.

Antibiotic guideline compliance

Twenty four patients (30.7%) of patients with mild disease received antibiotics which would not be recommended in the IAP/APA guideline. All patients with severe disease received antibiotics and 14 of 17 (82%) of patients with moderate disease received antibiotics.

Outcome

Overall median episode-related in-patient stay was 11 (range 1 – 133) days. Median in-patient stay in patients with severe disease was 31 (8-89) days with 14 (0-46) of this being spent in critical care.

Patients with mild disease spent a median of 9 (1-52) days as in-patients with a median of 0 (0-6) in critical care. Overall episode-related death occurred in 4 patients giving a mortality rate of 3.6% with all these deaths occurring in patients with severe acute pancreatitis.

Discussion

This study is a selective audit of the management of patients with acute pancreatitis in a tertiary specialist HPB centre with special emphasis on antibiotic use. An important potential methodological limitation is that it can be difficult to ascertain why any given individual was prescribed antibiotics in a given setting and this should be borne in mind in particular in relation to guideline compliance in this disease of considerable complexity.

In relation to the findings of this study it is apparent that patients who are transferred for tertiary care comprise a discrete subgroup of patients with acute pancreatitis. As expected, they represent cases of greater severity, and correspondingly the antibiotic use is higher and hospital stay is more prolonged.

Sixty five (58.5%) received antibiotics. Twenty four (30.7%) of patients with mild acute pancreatitis received antibiotics in the absence of any recorded intercurrent infection suggesting that this use was not in compliance with IAP/APA guidelines. Assessment of compliance in patients with severe acute pancreatitis is more problematic: although all patients with severe disease received antibiotics it is difficult to be certain with precision whether use was for documented infection.

When dichotomized by index or tertiary admission there was significantly more antibiotic use in patients who were tertiary transfers compared to those having their index admission to the centre (40.9 sd 37.1 person days vs 10.2 sd 8.9 person days; $P<0.005$). It should also be noted that these data do not include antibiotic use in tertiary transfer patients prior their transfer. In keeping with the prolonged in-patient stay seen in patients with severe acute pancreatitis, the majority of patients had more than one regimen of antibiotics with 10.8% receiving three courses.

The study shows that there is substantial use of antibiotics during the clinical course of acute pancreatitis. First, there seems to be overuse of antibiotics in patients with mild acute pancreatitis. In this setting, unless there is an indication for use of antibiotics for treatment of intercurrent infection there is no benefit from antibiotic use and a risk of harm. With respect to patients with severe disease, when

considering the multiple antibiotic regimens used there is a need for continued vigilance and precision in use of antibiotics. Multiple courses of broad-spectrum antibiotics create a high risk of encouraging emergence of resistant flora in a subset of patients with severe disease and physiological impairment.

In summary, this study examines a very common issue in everyday clinical management: that of antibiotic use in acute pancreatitis. In the context of the healthcare system wherein the study was set there is evidence of over-use of antibiotics in patients with mild acute pancreatitis. Although antibiotics are a necessary component of treatment in patients with severe acute pancreatitis, better consideration must be given to identification of prophylaxis or therapy as indication of use and in relation to repeated courses of broad-spectrum antibiotics there must be a clear indication for use. This audit highlights areas of potential inappropriate use. The study shows the need for better adherence to guidelines. Re-audit after better dissemination of the information contained in the IAP/APA guidelines is planned.

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Table 1: Patient characteristics and Treatment (categorical variables)

		Total		Index admissions to MRI		Tertiary referrals.		
		Count	(%)	Count	(%)	Count	(%)	p (2-s)+
Gender								
	Male	62	(55.9%)	41	(51.3%)	21	(67.7%)	0.139
	Female	49	(44.1%)	39	(48.8%)	10	(32.3%)	
Admission MODS score								
	0	57	(49.4%)	39	(49.4%)	18	(64.3%)	0.062
	1	29	(27.8%)	22	(27.8%)	7	(25.0%)	
	2	11	(10.1%)	8	(10.1%)	3	(10.7%)	
	3	4	(5.1%)	4	(5.1%)	0	(0.0%)	
	4	3	(3.8%)	3	(3.8%)	0	(0.0%)	
	5	2	(2.5%)	2	(2.5%)	0	(0.0%)	
	6	1	(1.3%)	1	(1.3%)	0	(0.0%)	
Aetiology								
	Not recorded	5	(5.0%)	4	(5.0%)	1	(3.2%)	0.962
	Biliary	53	(48.8%)	39	(48.8%)	14	(45.2%)	
	Alcohol	27	(22.5%)	18	(22.5%)	9	(29.0%)	
	Drug-related	6	(5.0%)	4	(5.0%)	2	(6.5%)	
	ERCP-induced	6	(5.0%)	4	(5.0%)	2	(6.5%)	
	Hypertriglyceridaemia	3	(3.8%)	3	(3.8%)	0	(0.0%)	
	Idiopathic	11	(10.0%)	8	(10.0%)	3	(9.7%)	
Pancreatitis CT severity								
	Mild	19	(29.7%)	18	(50.0%)	1	(3.6%)	**<0.001**
	Moderate	16	(14.4%)	4	(5 %)	12	(38.7%)	
	Severe	17	(15.3%)	6	(7.5%)	11	(35.5%)	
Pancreatitis clinical severity								
	Mild	78	(70.3%)	70	(87.5%)	8	(25.8%)	**<0.001**
	Moderate	17	(15.3%)	5	(6.3%)	12	(38.7%)	
	Severe	16	(14.4%)	5	(6.3%)	11	(35.5%)	
Interventions								
Radiology								
	None	86	(77.5%)	75	(93.8%)	11	(35.5%)	0.485
	Percutaneous drain	22	(20%)	3	(3.7%)	19	(61.3%)	
	Mesenteric Embolisation	5	(4.5%)	3	(3.8%)	2	(6.4%)	
Surgery								
	None	108	(97.3%)	80	(100.0%)	28	(90.3%)	**0.020**
	Necrosectomy	3	(2.7%)	0	(0.0%)	3	(9.7%)	
Endoscopy								
	None	90	(81.1%)	62	(77.5%)	28	(90.3%)	0.206
	ECRP ± stent	18	(16.2%)	16	(20.0%)	2	(6.5%)	
	Endoscopic necrosectomy	3	(2.7%)	2	(2.5%)	1	(3.2%)	
Antibiotic use								
	No	46	(41.4%)	44	(55%)	2	(6.4%)	**<0.001**
	Yes	65	(58.5%)	36	(45%)	29	(93.5%)	

Table 2: Patients' characteristics and Treatment (continuous variables)

Variables	Total (N=111)		MRI (n=80)		Referral (n=31)		Referral-MRI		
	Mean	SD	Mean	SD	Mean	SD	Difference	95%CI+	p(2-s)+
Age	55.3	18.6	55.6	20.0	54.3	14.7	-1.3	(-8. to 5.4)	0.712
Scoring and blood tests on admission									
APACHE II	6.4	3.3	6.1	3.5	7.1	2.7	1.1	(-0.2 to 2.3)	0.112
Hb	124.1	25.8	134.9	20.5	96.0	14.5	-38.9	(-45.5 to -32.2)	**<0.001**
WBC	13.6	7.0	12.7	4.8	16.1	10.4	3.5	(-0.1 to 7.5)	0.101
Amylase	853.2	929.8	987.5	961.1	190.7	226.2	-796.8	(-1041.4 to -556)	**<0.001**
Urea	6.0	3.9	5.8	3.4	6.5	5.0	0.8	(-1.1 to 2.8)	0.445
Creatinine	96.8	88.3	103.0	99.6	80.5	45.5	-22.5	(-50.5 to 3.)	0.114
Bilirubin	25.0	39.5	29.4	45.2	13.8	14.0	-15.6	(-27.3 to -5.3)	**0.019**
Alkaline phosphatase	159.1	147.7	134.6	91.7	221.5	227.5	86.8	(11.2 to 175.2)	0.057
Albumin	29.8	9.7	34.0	7.4	19.0	5.9	-15.0	(-17.6 to -12.4)	**<0.001**
CRP	107.2	126.9	71.9	109.0	196.1	126.7	124.3	(73.8 to 175.)	**<0.001**
Severity									
Delay to first CT in MRI (days)	4.6	4.7	4.1	4.3	5.3	5.1	1.2	(-1. to 3.6)	0.300
CT severity index (Balthazar)	4.9	3.4	3.1	2.5	7.3	2.8	4.3	(2.9 to 5.5)	**<0.001**
Antibiotics									
Person-days of antibiotics*	23.9	29.7	10.2	8.9	40.9	37.1	30.7	(17.1 to 46.2)	**0.005**
Hospital stay									
HDU stay (days)**	1.1	5.1	0.1	0.8	3.8	9.4	3.6	(0.6 to 7.6)	0.116
ITU stay (days)***	1.2	5.4	0.1	0.4	4.2	10.1	4.1	(0.9 to 8.3)	0.081
Total stay (days)	18.4	23.0	12.2	10.2	35.9	36.5	23.7	(11.1 to 38.3)	**0.015**

+ bootstrapped estimation

* In patients receiving antibiotics

**HDU= High Dependency Unit with non-invasive ventilatory support available.

***ITU=Intensive Care Unit with invasive (endotracheal) ventilatory support and renal replacement therapy available.

Table 3. Antibiotic use and outcome in mild, moderate and severe acute pancreatitis

	Pancreatitis clinical severity			
	Mild	**Moderate**	**Severe**	**Total**
Number of Patients (n)	78 (70%)	16 (14%)	17 (15%)	111
Antibiotic use	34 (44%)	13 (81%)	17 (100%)	64 (57.6%)
Indication not related to pancreatitis:	10 (13%)	2 (15%)	3 (18%)	15 (14%)
Cholecystitis	1	0	0	1
Cholangitis	1	0	0	1
Chest infection	0	1	1	2
Urinary tract infection	3	0	0	3
MRSA/VRE/CPE*	2	0	2	4
Clostridium difficile infection	1	1	0	2
Post-ERCP prophylaxis	2	0	0	2
Hospital stay (days - median/range)				
Total	9 (1-52)	23 (2-133)	31 (8-89)	11 (1-133)
High dependency /Intensive care unit	0 (0-6)	0 (0-24)	14 (0-46)	0 (0-46)
Mortality	0	0	4 (23.5%)	4 (3.6%)

Table 4: Frequency of use of antibiotics

	Count	(%)
Use of antibiotic regimens		
Amoxicillin + Clavulanic acid	30	(27.0%)
Ciprofloxacin	11	(9.9%)
Clarythromycin	1	(0.9%)
Colistin	2	(1.8%)
Fidaxomicin	1	(0.9%)
Flucloxacillin	1	(0.9%)
Fluconazole	4	(3.6%)
Gentamycin	6	(5.4%)
Meropenem	21	(18.9%)
Metronidazole	22	(19.8%)
Moxifloxacin	1	(0.9%)
Penicillin V	1	(0.9%)
Piperacillin + Tazobactam	27	(24.3%)
Vancomycin	2	(1.8%)
Teicoplanin	3	(2.7%)
Tigecycline	9	(8.1%)
Number of antibiotic regimens per patient		
0	53	(47.7%)
1	20	(18.0%)
2	14	(12.6%)
3	12	(10.8%)
4	5	(4.5%)
5	5	(4.5%)
6	2	(1.8%)
7	1	(0.9%)

Table legends

Legend table 1

+ Unordered categorical data MRI vs. Referral: Fisher's exact test; Ordered categorical data MRI vs. Referral: exact test for linear association. Admission MODS score for tertiary referral patients is calculated from point of admission to the tertiary care specialist unit at MRI and not from time of admission (admission MODS scores for these patients not available).

Legend Table 2

Hb = Haemoglobin (g/L); WBC = White Blood Cell Count (x 10^9/L); CRP = C-reactive protein (international units).

Legend table 3

***** MRSA: Methicillin Resistant Staphylococcus Aureus, VRE: Vancomycin Resistant Enterococci,

CPE: Carbapenemase-producing Enterobacteriaceae