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Summary of the Clinical Pharmacist's Role in the Management of Acute Pancreatitis: A Clinical Review

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ABSTRACT

Introduction: The role of the clinical pharmacist in the management of acute pancreatitis has not been researched extensively, and only a few published studies on the topic can be found. This clinical review presents all pertinent published data and serves as a guide for clinical pharmacists who participate in the management of patients with acute pancreatitis. **Methods:** An extensive literature search was conducted on PubMed from 1990 to 2021 to retrieve relevant studies focusing on the role of the clinical pharmacist in the treatment of acute pancreatitis.**Results:** An analysis of the medications that are associated with acute pancreatitis is presented, highlighting the responsibility of the pharmacist to conduct a thorough medication investigation in order to identify a possible drug-induced acute pancreatitis. Medical management of acute pancreatitis, mainly fluid therapy, is an area where a clinical pharmacist can appropriately intervene. Proper choice of fluid therapy and its rate, nutritional considerations, pain management and antibiotic use, are all important to consider for a successful treatment with minimal adverse effects. It is well documented in the literature that clinical pharmacists can decrease hospital costs. Discharge counseling performed by a clinical pharmacist has been shown to increase patient compliance and decrease both readmission rates and follow-up physician visits. **Conclusion:** The clinical pharmacist, as the primary drug expert, can identify medication-induced pancreatitis, diminish the use of unnecessary antibiotics, improve patient care and decrease the overall costs.

Keywords: acute pancreatitis, adverse drug reaction, clinical pharmacist, pharmacist intervention, pharmaceutical care.

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Introduction

Acute pancreatitis (AP) is the result of an inflammatory process within the pancreas [1]. The annual incidence of AP ranges from 13 - 45 per 100,000 people. Around 80% of patients present with a mild form of the disease; however, some patients suffer from more severe symptoms such as necrosis of the peri-pancreatic tissue, failure of multiple organs, and even coma and death [2,3]. Mild AP is associated with less than 5% mortality [4]. In severe cases, mortality can increase up to 25% [4]. Most patients who die have infected pancreatic necrosis [5]. Around 70% of AP is caused by alcohol abuse and/or gallstones [6]. Hypercalcemia, hypertriglyceridemia, malignancies, autoimmune diseases and medications are other potential etiologies for AP.

Diagnosing AP requires two out of the following three criteria to be present: abdominal pain, high serum lipase level (which is defined as at least three times the normal level), and characteristic findings of AP in abdominal imaging. When the diagnosis of AP is confirmed, a full medication history should be taken to rule out medication-induced AP [6].

The treatment of AP should involve a multidisciplinary collaboration between gastroenterology, nursing, clinical nutrition, and clinical pharmacy. A number of research studies that demonstrate the benefit of a clinical pharmacist's (CP) participation in clinical decision making were published [7]. Clinical activities performed by the CP include but are not limited to: taking a best possible medication history, developing effective and safe medication regimens, advising on the correct administration of drugs, and performing discharge counseling. The available evidence shows that CPs contribute substantially to the optimization of the use of antibiotics, to the minimization of adverse drug reactions and to a significant decrease in total treatment costs [8,9,10]. In a study published by the International Journal of Clinical Pharmacy in 2019, CP interventions in the treatment of AP reduces the costs of antibiotics by 23%, the costs of drugs by 12%, and the total hospitalization fee by 10% [11].

This review presents the CP's important contribution to AP management in the identification of manageable risk factors of AP and a thorough review of home medications to identify any possible drug-induced AP. The CP recommends patient-specific pharmacological treatment and supportive care, including fluid administration, nutritional support, pain management and appropriate antibiotic use based on the available published literature. Also, discharge counseling information provided to the patient is performed by the CP.

Methods

We conducted a literature search on PubMed from 1990 till March 2021 using the search terms: "pancreatitis", "pharmacy services", "pharmacists" and "drug-related side effects" and "adverse reactions". The literature search was restricted to studies published in English language. Eighty-one articles were selected to be included in this review.

Results

Summary of the clinical pharmacist's role in the management of acute pancreatitis

Identification of Risk Factors

The initial approach for the management of AP is identification of potential preventable risk factors. Alcohol consumption is the most common etiology of AP, causing around 25% to 41% of all cases [12]. By reviewing the patient social history, the CP should link alcohol consumption and AP [13,14]. Recent studies have shown an increase in the risk of developing AP when smoking and alcohol consumption are combined [15,16]. A prospective, multicenter, cohort of 145,886 participants showed that smoking, when added to heavy drinking, results in a significant higher risk of developing AP than either one alone (hazard ratio 2.06, 95% confidence interval 1.28-3.30) [16]. Smoking was also identified as a sole risk factor for AP [17]. The CP plays a fundamental role in patient

counseling on smoking cessation, as well as reducing alcohol intake [18]. Another less common causative factor is type II diabetes mellitus, correlating with a small but significantly higher risk of developing AP [19,20].

Review of Medications as Potential Causative Agents

Drug-induced AP can be considered after ruling out gallstone pancreatitis and ethanol-induced pancreatitis [21]. It is recommended to switch or stop any medication potentially causing AP to another drug class if possible [22]. Drug induced AP accounts for around 5% of all AP cases [23]. There are multiple mechanisms by which medications can cause AP (figure 1) [23,24,25].

According to the evidence-based review published by Badalov et al, drug-induced AP is categorized into 5 classes (class Ia-Ib-II-III-IV) [24]. This classification is based on: the number of case reports, whether a re-challenge was done, and the timeline between the intake of the medication and the occurrence of AP. Classes I and II have the highest potential for causing AP (table 1).

Medications Frequently Associated with Drug-Induced Acute Pancreatitis

Valproic acid:

Valproic acid (VA) is classified as class Ia. VA's food and drug administration (FDA)-approved product labeling in the United States of America (USA) has two black box warnings: hepatic failure and pancreatitis [26]. AP can occur upon initiation of VA; but more commonly, after chronic use (defined as >3 months of use). The suggested mechanism of pancreatitis is damage to the pancreatic duct. This occurs due to free radical formation and/or the active toxic metabolite of VA, 2-propyl-4-pentenoic acid [22,27]. The toxic metabolite is more common in patients receiving concomitant potent enzyme inducers such as phenytoin, carbamazepine, or rifampin. The damage inflicted on pancreatic cells has a latency period between three to six months [24].

Pravastatin, Simvastatin and other statins

Pravastatin and simvastatin are classified as class Ia, atorvastatin as class III, rosuvastatin, lovastatin and fluvastatin as class IV. Statin-induced pancreatitis has been observed hours to years after the initiation of the medication [28,29]. Since the latency time is variable, it is theorized that the mechanism by which statins damage the pancreas is by direct damage to pancreatic cells [24].

Enalapril

Enalapril is classified as class Ia. There have been five documented enalapril-induced AP case reports [30,31,32,33,34], two of which were confirmed by a rechallenge [30,31]. The proposed mechanism of enalapril induced AP is the development of angioedema of the pancreatic duct and accumulation of bradykinin [23]. The latency period is broad and ranges between five days and one year [24].

Azathioprine:

Azathioprine (AZ) is classified as class Ib. A deficiency in the enzyme responsible for AZ metabolism, thiopurine S-methyltransferase (TPMT), can increase the risk of toxicity of AZ by decreasing its metabolism to inactive metabolites. Testing for this deficiency would help identify patients who are at a higher risk for developing myelosuppression, hepatotoxicity, and AP [35]. The first case report of AP caused by AZ was reported in 1972 [36]. The most recent study linking AZ and AP was a prospective analysis performed in 2016, and included 510 patients diagnosed with irritable bowel disease who were initiated on AZ. The study showed that 37 out of 510 (7.3%) patients developed AP, with a median duration of 21 days [37]. The latency period ranges between five days and one month [24,37].

Amiodarone

Amiodarone is classified as class Ib. It has three black box warnings in the FDA-approved labelling: hepatotoxicity, pulmonary toxicity and proarrhythmia [38]. There have been three case reports of amiodarone induced AP [39,40,41]. Famularo et al described a patient who

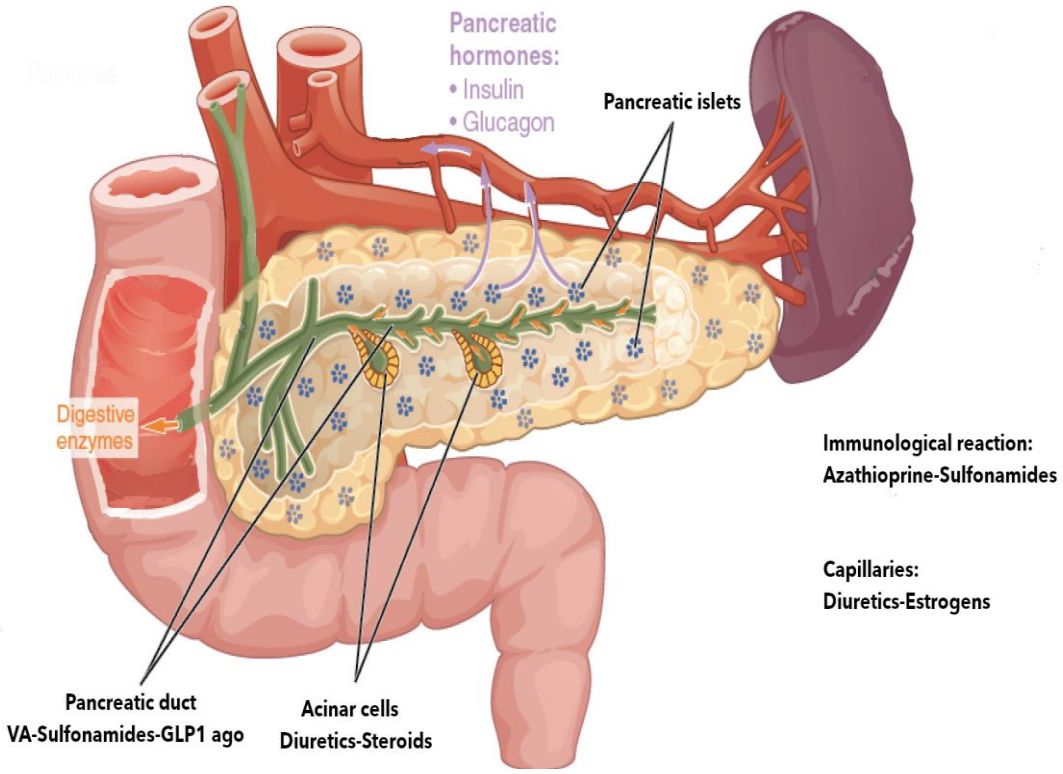

Figure 1. Mechanisms of drug-induced acute pancreatitis VA: valproic acid; GLP1 ago: glucagon like peptide-1 agonist; sulfonamides: sulfamethoxazole-mesalamine-sulfasalazine; diuretics: furosemide-hydrochlorothiazide

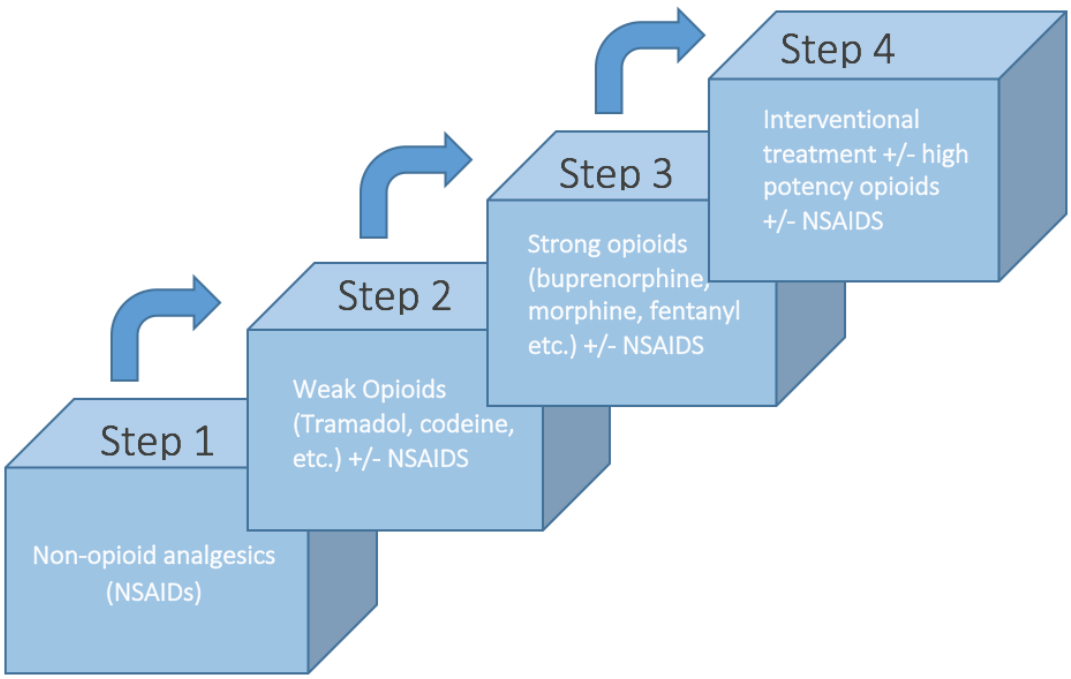

Figure 2. The modified World Health Organization (WHO) analgesia ladder NSAIDS: Non-steroidal anti-inflammatory drugs

Table 1. Summary of drug-induced pancreatitis

Class Ia	Class Ib	Class II	Class III	Class IV
Bezafibrate	ATRA	Acetaminophen	Alendronate	ACTH
Cannabis	Amiodarone	Chlorothiazide	Atorvastatin	Ampicillin
Carbimazole	Azathioprine	Didanosine	Carbamazepine	Benazepril
Codeine	Clomiphene	Erythromycin	Captopril	Betamethasone
Dapsone	Dexamethasone	Estrogen	Ceftriaxone	Capecitabine
Enalapril	Ifofamide	L-Asparginase	Chlorthalidone	Cisplatin
Furosemide	Lamivudine	Pegaspargase	Cimetidine	Colchicine
Isoniazid	Losartan	Propofol	Clarithromycin	Cyclophosphamide
Mesalamine	Lynesterol	Tamoxifen	Cyclosporin	Cyproheptadine
Methyldopa	6-MP		Gold	Diclofenac
Metronidazole	Methimazole		Hydrochlorothiazide	Diphenoxylate
Pentamidine	Nelfinavir		Indomethacin	Doxorubicin
Pravastatin	Norethindrone/		Interferon/Ribavirin	DPP-4 inhibitors
Procainamide	Mestranol		Irbesartan	Ethacrynic Acid
Simvastatin	Omeprazole		Isotretinoin	Famciclovir
Stibogluconate			Ketorolac	Finasteride
Sulfamethoxazole			Lisinopril	5-FU
Sulindac			Metolazone	Fluvastatin
Tetracycline			Metformin	Gemfibrozil
Valproic Acid			Minocycline	GLP-1 receptor agonists
			Mirtazapine	Il-2
			Naproxen	Ketoprofen
			Paclitaxel	Lovastatin
			Panotanib	Mefenamic Acid
			Prednisone	Nitrofurantoin
			Prednisolone	Octreotide
				Penicillin
				Propoxyphene
				Ramipril
				Ranitidine
				Rifampin
				Risperidone
				Ritonavir
				Rosuvastatin
				Sertraline
				Tacrolimus
				Vincristine

ATRA: all-trans-retinoic acid; 6-MP: 6-mercaptopurine; ACTH: adrenocorticotropic hormone; DPP-4: dipeptidyl peptidase-4; 5-FU: 5-fluorouracil; GLP-1: glucagon-like peptide-1; IL-2: interleukin-2

developed AP after receiving 600mg of amiodarone daily. A re-challenge with a reduced dose of 200mg did not cause a recurrence of AP [41]. Therefore, it is suggested that the loading dose of amiodarone can increase the risk AP. The latency period is few days after initiation of therapy [24].

Treatment Approach for Acute Pancreatitis:

The CP should have a comprehensive treatment approach for patients diagnosed with AP. It consists of five important components: (1) fluid management, (2) nutritional support, (3) pain management, (4) appropriate antibiotic use, and (5) patient counseling on discharge.

Appropriate Fluid Management and Nutritional Support

AP results in activation of inflammatory markers and hypovolemia can occur due to third spacing [42]. Thus, hydration with intravenous fluids is the mainstay of therapy in the first 12-24 hours [43]. Two randomized controlled trials showed that the inflammatory response was significantly decreased in patients who were treated with lactated ringers (LR) as compared to other hydration solutions [44,45]. The 2018 American Gastroenterological Association (AGA) guidelines for the treatment of AP recommends either normal saline (NS) 0.9% or LR solution as first line fluid therapy [43]. AP due to hypertriglyceridemia is relatively less common; it only accounts for approximately 3%–4% of all cases. A 5% dextrose solution is not recommended in cases of hypertriglyceridemia as dextrose is metabolized by the liver into fatty acids [46]. A goal directed strategy is used for fluid administration, with an initial rate of 5 mL/Kg/hr (with either LR or NS 0.9%) until resuscitation goals are achieved [4,43].

Historically, patients with AP were kept on empty stomach until normalization of the pancreatic enzymes [47]. This practice has changed in the past several years [12]. Now, patients can be initiated directly on oral feeding provided that they don't complain from abdominal pain, nausea or vomiting [48]. Initiation of feeding with a low-fat solid diet appears to be as safe and effective as a liquid diet [49]. On the other hand, in patients with moderate to severe AP, enteral nutrition with a low-fat formula using a nasojejunal feeding tube is recommended upon admission [12]. Provided that the patient is hemodynamically stable, it is recommended to use enteral feeding over parenteral nutrition. Enteral nutrition is less traumatic and is associated with a lower rate of infection and parenteral line-related complications [50]. Nevertheless, total parenteral nutrition (TPN) may be required in some patients. It is mainly recommended for patients whose daily caloric requirement is not sufficiently provided with enteral nutrition alone, or in patients who are hemodynamically unstable and cannot maintain jejunal access [51].

The CP participates in the development of an individualized nutritional care plan using TPN for patients with AP [52]. TPN should have a low fat content sufficient to avoid essential fatty acids deficiency (around 0.8 g/Kg per day) [51]. The use of lipid infusions during AP is safe in the absence of hypertriglyceridemia [51]. Thus, the CP should consistently monitor the triglyceride blood level.

Pain Management

In AP, pain is considered as both a diagnostic and a prognostic factor [53]. The first step in successful pain management in AP is early and aggressive fluid resuscitation [54]. Fluid resuscitation decreases the hemoconcentration and may alleviate pain [54]. Early enteral feeding may also reduce the intensity and duration of pain in AP [55].

In 1986, the World Health Organization (WHO) created a ladder for the management of cancer related pain, in order to guide appropriate analgesic use. This ladder was modified to expand its recommendations to include non-cancer related pain (figure 2) [56]. The WHO analgesic ladder consists of four steps. Step one starts with non-opioid analgesics, such as NSAIDS for mild pain. The pain ladder gradually adds on weak opioids, and then potent opioids

(e.g. morphine and fentanyl) depending on the severity of pain. Patients with AP usually present with moderate to severe pain; thus, opioid analgesics may be indicated. Previously, the systematic administration of opioid analgesics, especially morphine, was thought to be associated with the dysfunction of the sphincter of Oddi [57]. However, several subsequent studies have shown that morphine has no proven significant adverse effect on the course of AP and the practice of avoiding opioids in AP should be reconsidered [58,59,60,61]. Opioid administration is recommended for the shortest duration possible, and continuous monitoring for the side effects (respiratory and cardiovascular depression, constipation) should be performed by the CP.

Appropriate Antibiotic Use

Antibiotic prophylaxis in AP is not routinely recommended. Two meta-analyses involving 12 studies concluded that antibiotic prophylaxis did not prevent infection of pancreatic necrosis and had no effect on mortality rate [62,63]. Stopping the unjudicial use of antibiotics administered for patients diagnosed with AP is a priority for the CP. Preventing the use of unnecessary antibiotics is a good antimicrobial stewardship practice to minimize future antimicrobial resistance [64].

In certain patients with AP, antibiotics are indicated. Empirical antibiotics should be prescribed in suspected or proven infected pancreatic necrosis (IPN). Since IPN is associated with a high mortality rate, appropriate and timely antibiotic administration is recommended together with surgical intervention [65]. The most commonly isolated bacterial micro-organisms in IPN are the gut flora, mainly Gram negative (*Escherichia coli* and *Klebsiella* species) and anaerobic (*Bacteroides fragilis*) bacteria [66,67,68]. Adequate penetration is achieved with piperacillin, imipenem/cilastatin, ciprofloxacin, and cephalosporins [69]. The combination of ciprofloxacin and metronidazole or imipenem/cilastatin are the recommended empiric antibiotics for IPN with proven efficacy and acceptable safety [70]. After the identification of the micro-organism(s) and its/their susceptibilities from the surgical drainage culture, de-escalation to an appropriate narrow spectrum agent is recommended if possible [71].

Patient Counseling on Discharge

Patient counseling prior to hospital discharge is essential to ensure appropriate patient follow-up after discharge and has been shown to decrease readmission rates [11]. Patient counseling includes a thorough review of all discharge medications, including medications the patient was taking prior to hospital admission. The patient, using the teach-back method, is asked to repeat the pertinent information delivered by the CP [72]. All patients diagnosed with AP should be advised to follow a low fat diet in order to decrease the pressure on the pancreas to produce more lipase [73]. Diabetic patients should have a low carbohydrate diet and are advised to lose weight when needed [74]. Risk factors that increase a patient's risk for developing AP, such as alcohol ingestion and smoking, should also be addressed. If the patient is a smoker, it is recommended that the CP follows the 5 A's (ask, advise, assess, assist, arrange) intervention for smoking cessation [75]. Referral and pharmacological therapy for smoking cessation are recommended when appropriate.

Finally, due to a high recurrence rate of AP (17-22%) [76], the CP should highlight the importance of the follow-up physician clinic visit, which can be scheduled as early as one-week post discharge for severe AP [70].

Discussion

The published literature highlights the importance of the CP's participation in improving disease prevention and treatment, in reducing medication errors, and in cost optimization. Clinical pharmacists work closely with other health-care professionals and caregivers to ensure appropriate medication use. This is

achieved by evaluating medication orders daily for appropriateness, and recommending any necessary modifications to the health-care team. Medication-induced AP is an underestimated etiology. The CP's role, as the primary medication expert, will aid in the identification of drug-induced AP. Fluid management remains to be the mainstay of therapy for AP. LR or NS are the preferred fluids for hydration with an initial infusion rate is 5 ml/Kg/hr. Following the initiation of treatment, close monitoring of electrolytes is recommended, especially when NS 0.9% is used, as the patient may develop hypernatremia and/or hyperchloremic metabolic acidosis [44,77]. In addition, the CP should monitor kidney function for any changes in renal function and the rate of infusion time. Low-fat formulas of enteral feeding are preferred to prevent further pancreas damage. Enteral feeding preserves the gastrointestinal tract mucosa and prevents disruption and translocation of bacterial organisms that invade necrotic tissues in the pancreas; thereby, preventing infected pancreatic necrosis [78]. In case TPN is indicated, The CP will recommend patient-specific feeding formulations and will set the rate of administration. The CP can also participate in recommending the appropriate time of initiation, modification, or discontinuation of TPN based on the patient's clinical status, disease severity, and accessibility of the different routes of administration.

The CP also plays an integral role in dosing and monitoring of opioids. As the primary drug expert, the CP can recommend dosing regimens, opioid conversions of equivalent doses, side-effects monitoring, and de-escalation of pain medications when indicated. Frequent blood pressure, heart rate, and respiratory rate monitoring is recommended as opioids can cause cardiac and respiratory depression [79]. Opioid-induced constipation and decreased GI transit time may be mitigated with stimulant laxatives [80]. In case of IPN, prescribed antibiotics should have Gram-negative and anaerobic coverage. Antibiotics with adequate penetration into the pancreas are recommended to reach a concentration above the minimal inhibitory concentration (MIC) of the micro-organism. Although aminoglycosides provide excellent Gram negative coverage for patients with IPN, their poor penetration to the pancreas prohibits their clinical use for this indication [70,81]. The CP should counsel patients on lifestyle adjustments post discharge. A low-fat diet, smoking cessation, and alcohol rehabilitation/abstinence should be recommended during the counseling session. The CP should also stress on the importance of the follow-up abdominal CT, when ordered, for the post-discharge physician visit.

Our clinical review has several limitations. The published evidence on the specific role of the CP for the treatment of AP is scarce. Further evaluative studies are needed to better assess the role of the clinical pharmacist in the management of acute pancreatitis. We did not use multiple search engines; we only chose PubMed for the literature search. Another limitation of our clinical review is the inclusion of published articles only in the English language.

Conclusion

The clinical pharmacist's role is important in ensuring an appropriate, safe, and cost-effective treatment plan for patients with AP. The CP's interventions in the management of AP can reduce the misuse of antibiotics and medication costs, and can improve patient outcomes pre- and post- hospital discharge.

References

1. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
2. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155-65.
3. Banks PA, Freeman ML, Practice Parameters Committee of the American College of G. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379-400.

4. Hines OJ, Pandol SJ. Management of severe acute pancreatitis. BMJ. 2019;367:l6227.
5. Gravante G, Garcea G, Ong SL, Metcalfe MS, Berry DP, Lloyd DM, et al. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. Pancreatology. 2009;9(5):601-14.
6. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. World J Gastroenterol. 2009;15(12):1427-30.
7. Kaufmann CP, Stampfli D, Hersberger KE, Lampert ML. Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. BMJ Open. 2015;5(3):e006376.
8. Yang P, Jiang S-P, Lu X-Y. Effectiveness of continuous improvement by a clinical pharmacist-led guidance team on the prophylactic antibiotics usage rationality in intervention procedure at a Chinese tertiary teaching hospital. Ther Clin Risk Manag. 2017;13:469-76.
9. Malfara M, Pernassi M, Aragon D, Carlotti A. Impact of the clinical pharmacist interventions on prevention of pharmacotherapy related problems in the paediatric intensive care unit. Int J Clin Pharm. 2018;40(3):513-9.
10. Yang H, Li L, Hu X, Wang W, Yang X, Liu H, et al. Impact of pharmacist-led post-transplant medication management for kidney transplant recipients: A retrospective pre- and post-intervention study. J Clin Pharm Ther. 2019;44(4):603-10.
11. Niu JL, Ding YL, Ju F, Lu T, Xue T, Chen KX, et al. Effect of clinical pharmacist intervention on the treatment of acute pancreatitis. Int J Clin Pharm. 2019;41(6):1652-7.
12. Tenner S, Baillie J, DeWitt J, Vege SS, American College of G. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400-15; 16.
smoking cessation and weight management, including meta-analysis for smoking cessation. BMJ Open. 2016;6(2):e009828.
13. Lowenfels AB, Maisonneuve P, Sullivan T. The changing character of acute pancreatitis: epidemiology, etiology, and prognosis. Curr Gastroenterol Rep. 2009;11(2):97-103.
14. Gullo L, Migliori M, Olah A, Farkas G, Levy P, Arvanitakis C, et al. Acute pancreatitis in five European countries: etiology and mortality. Pancreas. 2002;24(3):223-7.
15. Setiawan VW, Monroe K, Lugea A, Yadav D, Pandol S. Uniting Epidemiology and Experimental Disease Models for Alcohol-Related Pancreatic Disease. Alcohol Res. 2017;38(2):173-82.
16. Setiawan VW, Pandol SJ, Porcel J, Wilkens LR, Le Marchand L, Pike MC, et al. Prospective Study of Alcohol Drinking, Smoking, and Pancreatitis: The Multiethnic Cohort. Pancreas. 2016;45(6):819-25.
17. Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169(11):1035-45.
18. Brown TJ, Todd A, O'Malley C, Moore HJ, Husband AK, Bambra C, et al. Community pharmacy-delivered interventions for public health priorities: a systematic review of interventions for alcohol reduction,
19. Shafqet M, Sharzehi K. Diabetes and the Pancreatobiliary Diseases. Curr Treat Options Gastroenterol. 2017;15(4):508-19.
20. Gonzalez-Perez A, Schlienger RG, Rodriguez LA. Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study. Diabetes Care. 2010;33(12):2580-5.
21. Tenner S. Drug induced acute pancreatitis: does it exist? World J Gastroenterol. 2014;20(44):16529-34.
22. Jones MR, Hall OM, Kaye AM, Kaye AD. Drug-induced acute pancreatitis: a review. Ochsner J. 2015 Spring;15(1):45–51.
23. Spanier BW, Tuynman HA, van der Hulst RW, Dijkgraaf MG, Bruno MJ. Acute pancreatitis and concomitant use of pancreatitis-associated drugs. Am J Gastroenterol. 2011;106(12):2183-8.
24. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W, Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. 2007;5(6):648-61
25. Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. JAMA Intern Med. 2013;173(7):534-9.
26. BOXED WARNING. FULL PRESCRIBING INFORMATION [Internet]. Fda.gov. [cited 2020 Nov 22]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/018081s046_18082s031lbl.pdf
27. Bryant AE, 3rd, Dreifuss FE. Valproic acid hepatic fatalities. III. U.S. experience since 1986. Neurology. 1996;46(2):465-9.
28. Thisted H, Jacobsen J, Munk EM, Norgaard B, Friis S, McLaughlin JK, et al. Statins and the risk of acute pancreatitis: a population-based case-

control study. Aliment Pharmacol Ther. 2006;23(1):185-90.
29. Anagnostopoulos GK, Tsiakos S, Margantinis G, Kostopoulos P, Arvanitidis D. Acute pancreatitis due to pravastatin therapy. Jop. 2003;4(3):129-32.
30. Maringhini A, Termini A, Patti R, Ciambra M, Biffarella P, Pagliaro L. Enalapril-associated acute pancreatitis: recurrence after rechallenge. Am J Gastroenterol. 1997;92(1):166-7.
31. Carnovale A, Esposito P, Bassano P, Russo L, Uomo G. Enalapril-induced acute recurrent pancreatitis. Dig Liver Dis. 2003;35(1):55-7.
32. Madsen JS, Jacobsen IA. Angiotensin converting enzyme inhibitor therapy and acute pancreatitis. Blood Press. 1995;4(6):369-71.
33. Gonzalez Ramallo VJ, Muino Miguez A, Torres Segovia FJ. Necrotizing pancreatitis and enalapril. Eur J Med. 1992;1(2):123.
34. Birck R, Keim V, Fiedler F, van der Woude FJ, Rohmeiss P. Pancreatitis after losartan. Lancet. 1998;351(9110):1178.
35. Clunie GPR, Lennard L. Relevance of thiopurine methyltransferase status in rheumatology patients receiving azathioprine. Rheumatology (Oxford). 2004;43(1):13–8.
36. Nogueira JR, Freedman MA. Acute pancreatitis as a complication of Imuran therapy in regional enteritis. Gastroenterology. 1972;62(5):1040-1.
37. Teich N, Mohl W, Bokemeyer B, Bundgens B, Buning J, Miehlke S, et al. Azathioprine-induced Acute Pancreatitis in Patients with Inflammatory Bowel Diseases--A Prospective Study on Incidence and Severity. J Crohns Colitis. 2016;10(1):61-8.
38. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA. 2007;298(11):1312-22.
39. Bosch X, Bernadich O. Acute pancreatitis during treatment with amiodarone. Lancet. 1997;350(9087):1300.
40. Sastri GV. Gastrointestinal complications of amiodarone therapy. J Clin Gastroenterol. 1990;12:70-7.
41. Famularo G, Minisola G, Nicotra GC, De Simone C. Acute pancreatitis caused by amiodarone. Eur J Emerg Med. 2004;11(5):305-6.
42. Forsmark Ch E, Vege SS, Wilcox CM. Acute Pancreatitis. N Engl J Med. 2017;376(6):598-9.
43. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, Amer. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018;154(4):1096-101.
44. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011;9(8):710-7 e1.
45. Choosakul S, Harinwan K, Chirapongsathorn S, Opuchar K, Sanpajit T, Piyanirun W et al. Comparison of normal saline versus Lactated Ringer's solution for fluid resuscitation in patients with mild acute pancreatitis, A randomized controlled trial. Pancreatology. 2018;18(5):507-512.
46. Rui L. Energy metabolism in the liver. Compr Physiol. 2014;4(1):177-97.
47. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med. 1994;330(17):1198-210.
48. Eckerwall GE, Tingstedt BB, Bergenzaun PE, Andersson RG. Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery--a randomized clinical study. Clin Nutr. 2007;26(6):758-63.
49. Jacobson BC, Vander Vliet MB, Hughes MD, Maurer R, McManus K, Banks PA. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. Clin Gastroenterol Hepatol. 2007;5(8):946-51
50. Gupta R, Patel K, Calder PC, Yaqoob P, Primrose JN, Johnson CD. A randomised clinical trial to assess the effect of total enteral and total parenteral nutritional support on metabolic, inflammatory and oxidative markers in patients with predicted severe acute pancreatitis (APACHE II > or =6). Pancreatology. 2003;3(5):406-13.
51. Gianotti L, Meier R, Lobo DN, Bassi C, Dejong CH, Ockenga J, et al. ESPEN Guidelines on Parenteral Nutrition: pancreas. Clin Nutr. 2009;28(4):428-35.
52. Tucker A, Ybarra J, Bingham A, Blackmer A, Curtis C, Mattox T, et al. American society for parenteral and enteral nutrition (A.S.P.E.N.) standards of practice for nutrition support pharmacists. Nutr Clin Pract. 2015;30(1):139-46.
53. Schorn SC, Güralp O. Tieftrunk, Elke. Friess, Helmut. Demir, Ihsan Ekin. Pain Management in Acute Pancreatitis. Pancreapedia: Exocrine Pancreas Knowledge Base. 2015.
54. Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol. 2008;6(10):1070-6.
55. Petrov MS, McIlroy K, Grayson L, Phillips AR, Windsor JA. Early nasogastric tube feeding versus nil per os in mild to moderate acute pancreatitis: a randomized controlled trial. Clin Nutr. 2013;32(5):697-703.

56. Vargas-Schaffer G. Is the WHO analgesic ladder still valid? Twenty-four years of experience. Can Fam Physician. 2010;56(6):514-7, e202-5.
57. Helm JF, Venu RP, Geenen JE, Hogan WJ, Dodds WJ, Toouli J, et al. Effects of morphine on the human sphincter of Oddi. Gut. 1988;29(10):1402-7.
58. R. Jakobs, M. U. Adamek, A. C. Von. Buprenorphine or Procaine for Pain Relief in Acute Pancreatitis. A Prospective Randomized Study. Scandinavian Journal of Gastroenterology. 2000;35(12):1319-1323.
59. Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol. 2001;96(4):1266-72.
60. Peiro AM, Martinez J, Martinez E, de Madaria E, Llorens P, Horga JF, et al. Efficacy and tolerance of metamizole versus morphine for acute pancreatitis pain. Pancreatology. 2008;8(1):25-9.
61. Basurto Ona X, Rigau Comas D, Urrutia G. Opioids for acute pancreatitis pain. Cochrane Database Syst Rev. 2013(7):CD009179.
62. de Vries AC, Besselink MG, Buskens E, Ridwan BU, Schipper M, van Erpecum KJ, et al. Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: relationship between methodological quality and outcome. Pancreatology. 2007;7(5-6):531-8.
63. Mazaki T, Ishii Y, Takayama T. Meta-analysis of prophylactic antibiotic use in acute necrotizing pancreatitis. Br J Surg. 2006;93(6):674-84.
64. File TM, Jr., Srinivasan A, Bartlett JG. Antimicrobial stewardship: importance for patient and public health. Clin Infect Dis. 2014;59 Suppl 3:S93-6.
65. Rana SS. An overview of walled-off pancreatic necrosis for clinicians. Expert Rev Gastroenterol Hepatol. 2019;13(4):331-43.
66. Isenmann R, Friess H, Schlegel P, Fleischer K, Büchler MW. Penetration of ciprofloxacin into the human pancreas. Infection. 1994;22(5):343-6.
67. Seewald S, Groth S, Omar S, Imazu H, Seitz U, de Weerth A, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). Gastrointest Endosc. 2005;62(1):92-100.
68. Rao C, Bhasin DK, Rana SS, Gupta R, Gautam V, Singh K. Implications of culture positivity in acute pancreatitis: does the source matter? J Gastroenterol Hepatol. 2013;28(5):887-92.
69. Otto W, Komorzycki K, Krawczyk M. Efficacy of antibiotic penetration into pancreatic necrosis. HPB: the official journal of the International Hepato Pancreato Biliary Association. 2006;8(1):43-8.
70. Leppaniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, et al. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg. 2019;14:27.
71. De Waele JJ. Rational use of antimicrobials in patients with severe acute pancreatitis. Semin Respir Crit Care Med. 2011;32(2):174-80.
72. ASHP guidelines on pharmacist-conducted patient education and counseling. Am J Health Syst Pharm. 1997;54(4):431-4.
73. Lowe M S. Nutritional advice for prevention of acute pancreatitis: review of current opinion. Nutrition and Dietary Supplements. 2012;4:70-1.
74. Jordan MA, Harmon J. Pharmacist interventions for obesity: improving treatment adherence and patient outcomes. Integr Pharm Res Pract. 2015;4:79-89.
75. Black JH, 3rd. Evidence base and strategies for successful smoking cessation. J Vasc Surg. 2010;51(6):1529-37.
76. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, et al. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2016;14(5):738-46.
77. Pfortmueller CA, Funk GC, Reiterer C, Schrott A, Zotti O, Kabon B, et al. Normal saline versus a balanced crystalloid for goal-directed perioperative fluid therapy in major abdominal surgery: a double-blind randomised controlled study. Br J Anaesth. 2018;120(2):274-83.
78. Yi F, Ge L, Zhao J, Lei Y, Zhou F, Chen Z, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. Intern Med. 2012;51(6):523-30.
79. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):825-73.
80. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S, et al. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. Gastroenterology. 2019;156(1):218-26.
81. Buchler M, Malfertheiner P, Friess H, Isenmann R, Vanek E, Grimm H, et al. Human pancreatic tissue concentration of bactericidal antibiotics. Gastroenterology. 1992;103(6):1902-8.