REVIEW ARTICLE

Hemorrhagic Complications after Pancreatic Surgery: A Comprehensive Review of Literature

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ABSTRACT

Hemorrhage after pancreatic surgery is a common occurrence, accounting for 5-12% of post-pancreatectomy complications. Major risk factors for hemorrhage can be classified temporally as pre-operative, intra-operative, and post-operative, and include perioperative coagulopathy, technical failure of hemostasis at suture line, post-operative pancreatic fistulas grades B and C, biliary leakage, localized or intra-abdominal sepsis, higher age and Body Mass Index, and intraoperative transfusions, among others. Post-pancreatectomy hemorrhage can be mild or severe, with grading from A to C, and timing from early (within 24 hours) to late (after 24 hours): diagnostic and therapeutic modalities vary widely based on the grading and location of post-pancreatectomy hemorrhage, while non-operative management is sufficient for mild grade. A post-pancreatectomy hemorrhage, interventions such as angiography for extra-luminal and endoscopy for intraluminal hemorrhage are required for late grade B or C hemorrhage. Re-exploration to secure hemostasis is preferred in hemodynamically unstable patients, and is only used for late post-pancreatectomy hemorrhage after failure of less invasive modalities. Late post-pancreatectomy hemorrhage is associated with a poor prognosis, especially in low-flow centers. Careful monitoring for sentinel bleeding, as well as control over modifiable risk factors can help decrease the incident burden of post-pancreatectomy hemorrhage, thereby reducing long-term morbidity and mortality after pancreatic surgery.

INTRODUCTION

The pancreas has been described as "the most unforgiving organ in the human body," owing to its deep-seated location and numerous important neighboring structures- most of them vascular [1]. Common operative procedures dealing with the pancreas include pancreaticoduodenectomy (Whipple's procedure), and distal pancreatectomy; while indications for the former are limited to malignant lesions involving the head of pancreas and periampullary region, as well as refractory pain from chronic pancreatitis; pancreatic resections, with a paltry 25% attributed to distal pancreatectomy [2]. Total pancreatectomy, once the only procedure available to deal with malignant pancreatic tumors, has now largely been abandoned, despite research showing that it might have good long-term outcomes. Survival rates associated with this operation are still relatively low, with a 5-year survival rate of only 13% reported by a review of National Cancer Database [3] While modifications of pancreatectomy such as pylorus-preservation (PPPD-pylorus preserving pancreaticoduodenectomy), and subtotal stomach-preserving pancreaticoduodenectomy are increasingly gaining attention, their clinical validity against traditional Whipple pancreaticoduodenectomy still remains questionable [4]. Procedures such as pancreatic enucleation are associated with less blood loss, shorter operative period, ICU and hospital stay, and low rate of mortality; however, they can be performed only in a subset of the patients with pancreatic tumors and require advanced surgical specialization skills [5]. Indications for the latter are more extensive, dealing with solid and cystic tumors of the body and tail of the pancreas, as well as with pseudocysts or pancreatic fistulas arising from disruption in the afore-mentioned regions [1]. Pancreaticoduodenectomy accounts for the majority of pancreatic resections, with a paltry 25% attributed to distal pancreatectomy [2]. While modifications such as pylorus-preservation, and subtotal stomach-preserving pancreaticoduodenectomy are increasingly gaining attention, their clinical validity against traditional Whipple pancreaticoduodenectomy still remains questionable [3].

Postoperative complications are relatively still common after pancreatic surgeries, accounting for high morbidity and mortality rates. While perioperative mortality has been reduced to 5-10%, morbidity still ranges from 40-58% in most centers, being limited to 2-4% only in high volume centers with carefully selected patients, improved

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Abbreviations BMI body mass index; PPH post-pancreatectomy hemorrhage; POPFs postoperative pancreatic fistulas; SIRS systemic inflammatory response syndrome; ISGPS International Study Group of Pancreatic Surgery; PPPD pylorus preserving pancreaticoduodenectomy; PG pancreatogastrostomy; NOM: Non-Operative Management
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Table 1. Incidence and risk factors for various complications of pancreatic surgery.

Complication	Possible Risk Factors	Incidence
Delayed Gastric Emptying	Prior abdominal surgery, history of cholangitis, diabetes mellitus, pancreatic fistula with intra-abdominal fluid collection [2].	17% [7]
Biliary Leaks	-	1-2% [2]
Postoperative Pancreatic Fistula (POPF)	High BMI, preoperative jaundice, soft pancreas, narrow pancreatic duct, increased intraoperative blood loss, prolonged operative time, drain amylase >4000 on first postoperative day [8]	5-10% [8]
Post-pancreatectomy Hemorrhage (PPH)	Diameter of pancreatic duct, pancreatic fistula, intra-abdominal abscess [9], sepsis, soft consistency of pancreatic remnant, vascular hardening during lymphadenopathy leading to surgical trauma [10]	5-12% [11]

surgical techniques and perioperative care [6, 7, 8, 9]. Complications of pancreatic surgery range from delayed gastric emptying to biliary leaks, postoperative pancreatic fistulas (POPFs), and post-pancreatectomy hemorrhage (PPH). **Table 1** lists the incidence and risk factors for some of the major complications of pancreaticoduodenectomy.

PPH accounts for a high mortality rate after pancreatic surgery, ranging from 18-47% [10]. In centers lacking advanced instrumentation and skills, such as those in lower middle income countries, these complications are often undiagnosed and lead to significantly higher morbidity and mortality. It has been shown recently that PPH has low incidence and mortality rates in centers with high-volume of surgery [11, 12], and that such low rates can be achieved by avoiding reoperation in favor of interventional procedures (detailed below) whenever possible. The aim of this review is to outline the risk factors, diagnostic strategies, and management strategies for early and late PPH, as well as preventative methods that can be applied pre-, intra-, and post-operatively.

METHODS

Literature search was carried out using the keywords "pancreas," "pancreatic surgery," "pancreaticoduodenectomy," "hemorrhage," and "post-pancreatectomy hemorrhage". Out of 79 entries in PubMed database, 28 were chosen for relevance to current topic; these were supplemented by journal and book entries from a personal reference list. The majority of the incorporated studies were based on single or multi-centre series with varying number of patients.

REVIEW OF LITERATURE

Definition and Classification of PPH

In 2007, the International Study Group of Pancreatic Surgery (ISGPS) issued a consensus definition of PPH, based on three parameters: time of onset; location and cause; and severity. Based on time of onset, PPH can be classified into early and late, with the former occurring within the first 24 postoperative hours after the end of the index operation, and the latter occurring thereafter. On the basis of location, PPH is intraluminal (from areas of resection [pancreatic stump or retroperitoneum]; gastric/duodenal ulcer or diffuse gastritis; and hemobilia from prior endobiliary stents) or extraluminal (from arterial or venous blood vessels; suture lines of gut anastomoses; and eroded or ruptured pseudoaneurysms). PPH can be mild or severe: mild PPH involves small/medium volume blood loss with no clinical impairment and no need for re-operation; while severe PPH is characterized by large volume blood loss (Hb drop >3 g/dl), as well as clinical deterioration requiring >3 units packed cell transfusion as well as invasive treatment such as relaparotomy or angiographic embolization [13]. A critical appraisal of this definition showed that while the definition was reliable and feasible for clinical practice, it was associated with a high false positive rate of mild PPH, requiring a redefinition of mild PPH as an Hb drop of ≥ 3 g/dl with no significant clinical impairment, requiring no blood transfusions with >3 units of PRBCs and no interventional or therapeutic treatment. This slightly differs from the original definition, in which transfusion of 2-3 units of packed cells within 24 hours and 1-3 units after 24 hours is admissible in patients with mild clinical impairment [14].

Based on the criteria set above, the ISPGS classifies PPH into 3 grades **(Table 2)**. Diagnostic and management pathways vary for the different grades: while grade A has no major clinical impact, grade-C PPH has a dramatic impact on the management strategy, often necessitating prompt surgical or radiological intervention as well as committed ICU care [13]. More recent studies estimate that there is no overall clinical impact of grade A PPH, and therefore it should be removed from the ISPGS classification to avoid overestimation of the total PPH rate. They recommend a classification based on concomitant POPF, with categories including severe PPH without POPF; mild PPH with POPF; and severe PPH with POPF. This classification has been found to better predict mortality, duration of ICU stay, and need for relaparotomy in patients with PPH compared to the ISPGS classification [12]. However, since the ISPGS classification is still the widely used standardized classification to date, it will be followed for the purposes of this review.

Incidence and Risk Factors for PPH

Several retrospective studies have been carried out with variable sample sizes to calculate the incidence and identify risk factors for PPH. On average, the incidence ranges from 5-12% [11]; the incidence of early and late PPH varies among studies conducted before and after introduction of the ISPGS definition, due to different usages of these terms by various authors. Late PPH has a higher mean incidence, ranging from 70-90% [9, 10, 15, 16], and is associated with a high mortality rate from 11-20% [16].

Table 2. Grading of post-pancreatectomy hemorrhage.

Grade	Time of Onset, Location, and Severity	Clinical Condition
A	Early; Intra- or extraluminal; Mild	Well
B	a. Early; Intra- or extraluminal; Severe	Seldom life threatening, often patient is well/intermediate
	b. Late; Intra- or extraluminal; Mild	
C	Late; Intra- or extraluminal; Severe	Severe impairment, life threatening

Several studies have also reported the relative prevalence of PPH by grades. Grade C is the most prevalent grade of PPH, accounting for almost 70-90% of the cases of late PPH in the identified studies [9, 10, 15, 16]. One study reported a higher prevalence of grade A/B PPH with intraluminal hemorrhage, and grade C with extraluminal hemorrhage [16]; this has been confirmed by some other studies as well [17]. A remarkably high coincidence of POPF with PPH has also been reported, with figures approaching as high as 75% [18]; however, the exact temporal correlation between the two remains unknown [11].

A number of risk factors have been identified as responsible for PPH to some degree: these can be conveniently divided into pre-, intra- and post-operative factors. **Figure 1** describes some of these risk factors, which we discuss in detail below.

Early PPH mostly results due to technical failures of hemostasis at the anastomotic sites such as suture lines, or due to perioperative coagulopathy [18]. In one series of pancreatic resections, three major reasons for early PPH were identified as:

1. Technical failure of hemostasis in the operative field leading to extraluminal PPH

2. Hemorrhage from the suture line of gastroenteric or enteroenteric anastomosis, uniformly leading to intraluminal PPH

3. PPH from pancreaticoenteral anastomosis on the transection surface (after Whipple) or from the resection cavity (after surgery for chronic pancreatitis), leading either to intraluminal PPH presenting as hematemesis or melena, or as "false" extraluminal hemorrhage arising indirectly from an intraluminal bleeding site after bursting of the pancreaticojejunostomy [19].

In contrast, several risk factors have been identified for late PPH, with further categorizations as described in (**Figure 1)**. A retrospective cohort study of 500 patients at a hospital in Sweden identified operative time (in minutes), POPF Grades B and C, biliary leakage and gastrojejunostomy leakage as statistically significant risk factors for PPH grades B and C on univariate analysis; however, on multivariate analysis, only POPF grades B and C and bile leakage were found to be significant independent predictors of PPH [17]. Localized sepsis also plays a role in late PPH-this has been shown by a statistically significant association between MRSA in drain fluid after pancreatectomy and PPH [10]; the sepsis itself may be a result of pancreatic abscess, fistula, or bile leak [20]. In another series with over 1000 pancreatic resections, univariate risk factors for PPH grade C included higher age and BMI, high-risk histopathology, intraoperative transfusions, POPF, reconstruction by pancreatogastrostomy (PG), and portal venous and multivisceral resection; on multivariate analysis, male sex was an additional risk factor [16]. This study also identified pre-operative biliary drainage and operation in recent time period as protective factors against PPH. Very low hospital volume, vascular resections, and post-operative wound/intra-abdominal infections have also been identified as multivariate predictors for post-operative hemorrhage in another large series of 2548 patients [21]. Regional lymphadenectomy, as well as exocrine competency of the pancreatic remnant (which defines the potential for vascular erosion) are also contributory factors for delayed arterial hemorrhage after PD [22]. Perioperative clotting status, presence of comorbid conditions that affect blood clotting, and administration of intraoperative and postoperative transfusions are all risk factors that have been linked with PPH with variable evidence [16]. Perioperative antithrombotic treatment, while an effective deterrent against postoperative thromboembolism, is also an independent risk factor for developing PPH [23].

Given the large number of risk factors for late PPH, it is easily imaginable the extent of morbidity and mortality associated with it. Early PPH is associated with better prognostic outcomes; for late PPH, the earlier the diagnosis, the better is the associated outcome [21].

Diagnostic Tools for PPH

The diagnosis of PPH is based on clinical observation, as well as laboratory and radiological investigations-all these help in classifying PPH as either early or late; intraluminal or extraluminal; and mild or severe, according to the ISGPS criteria. Sentinel bleeding, a minor preliminary bleeding predicting the onset of PPH in a time frame of 6 hours to 10 days, is a prelude to arterial hemorrhage and must be carefully monitored [22]. Chen et al. have recently proposed an operational definition of sentinel bleeding as:

1. Intermittent and obvious hemorrhage from abdominal drains or GIT (manifesting as hematemesis or melena)

2. Drop in haemoglobin of ≥ 1.5 g/dl

3. Spontaneous stopping of bleeding without transfusion, or

4. Re-bleeding within an interval of at least 12 hours [24].

It appears, therefore, that sentinel bleeding must be carefully observed for, and if present, interventional preparations to deal with impending PPH must be made. Recurrent episodes of minor bleeding should also alert to the possibility of major arterial hemorrhage leading to hemorrhagic shock [25].

The ISGPS classification of PPH proposed different diagnostic consequences according to the grades of PPH: while observation, blood count, and ultrasonography with the occasional CT were considered enough for diagnosis of Grade A PPH; angiography, endoscopy, and CTA were vital adjuncts for the diagnosis of Grade-B & C PPH [13]. Intraluminal bleeding due to ulcers or wound opening can be excluded by the use of upper GI endoscopy; CT should be used to monitor suspected pseudo-aneurysm of the main visceral artery [22, 26]. In hemodynamically stable patients, CTA is recommended for every suspected/actual PPH, because of its high sensitivity in diagnosing intraluminal/extraluminal hemorrhages as well as pseudo-intraluminal hemorrhages [27]. Diagnostic angiography is limited in certain situations, especially in the presence of hemodynamic instability; when performed, however, it has been reported to localize almost 90% of bleeding sources [18]. A proposed algorithm for diagnosis and categorization of PPH is presented in **(Figure 2)** [27].

Management Strategies for PPH

In this review we compare four of the most commonly used strategies for management and control of PPH, with respect to their efficacy based on location and grade of PPH. These include: Non-operative Management, Surgery with re-exploration, Interventional Endoscopy and Interventional Angiography with Vascular Embolization

These techniques are discussed in detail below:

Non-Operative Management (NOM): NOM is the standard of care for early mild PPH, with no clinical impairment and minimal drop in Hb or need for transfusion. The principles of NOM are the same as elsewhere in the surgical arena: regular monitoring of vitals and laboratory investigations is carried out, with focus on drain fluids as well to locate early sentinel bleeds. If necessary, transfusion of fluids/blood and/or coagulation factors can be carried out as well [27]. NOM can be carried out in high-dependency units (HDUs), as well as in ICUs if the need arises. Mild PPH is generally considered to have no significant clinical impacts, and as such should not be a cause of delay in discharge from hospital [13]. Cold saline injections into stomach tube, adrenaline, and hemocoagulase have recently been introduced as adjuncts to NOM, with varying success [24].

Surgical management: For hemodynamically unstable patients, exploratory salvage laparotomy with abdominal packing, and if possible, intraoperative angiography, is the standard of care [27]. In hemodynamically stable patients, laparotomy is increasingly being preferred as a last-ditch stand procedure, with interventional angiography and endoscopy being given precedence over it [16]. In severe early PPH, re-exploration is the procedure of choice, because a surgically correctable cause of bleeding is most likely to be found [16, 28]. Re-exploration carries with it a risk of late PPH: in such a scenario, surgical exploration is technically challenging, because of post-surgical adhesions, as well as difficult access to the bleeding vessels under the anastomoses. Secondary complications

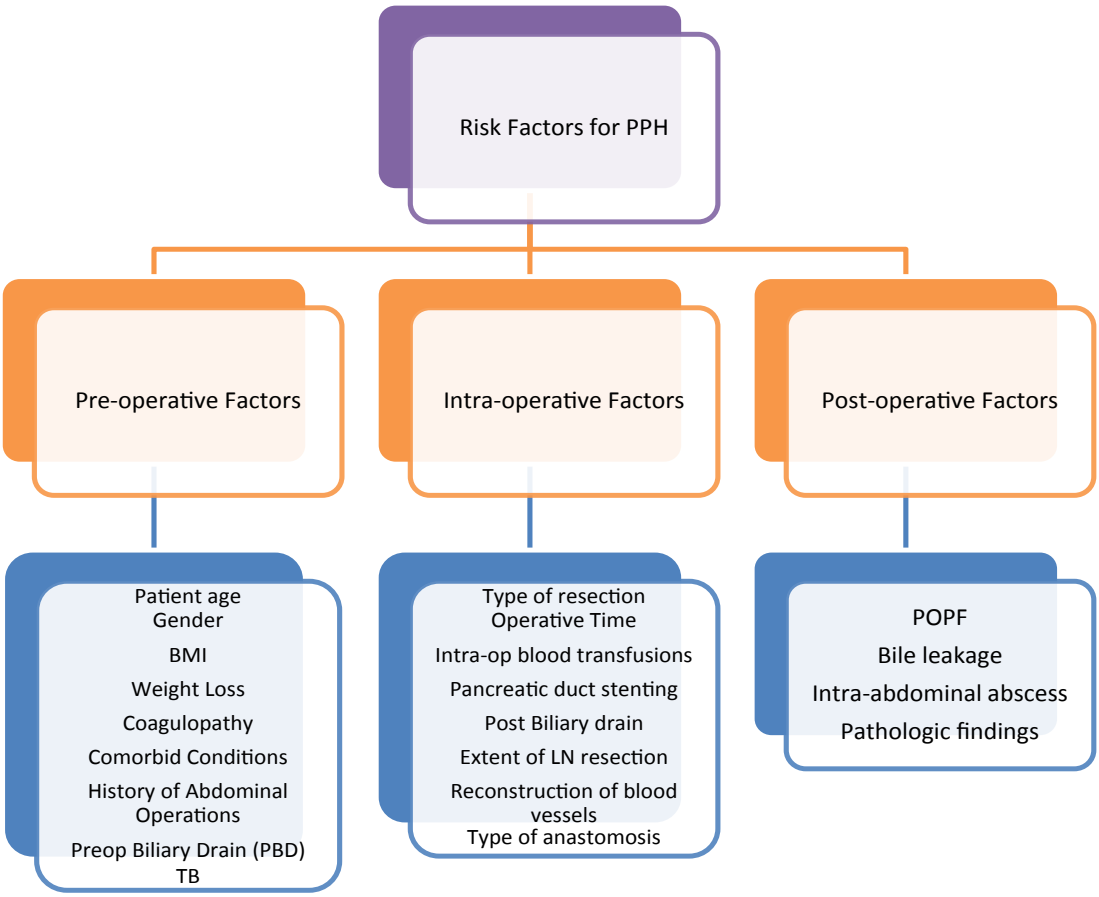

Figure 1. Classification of risk factors for PPH.

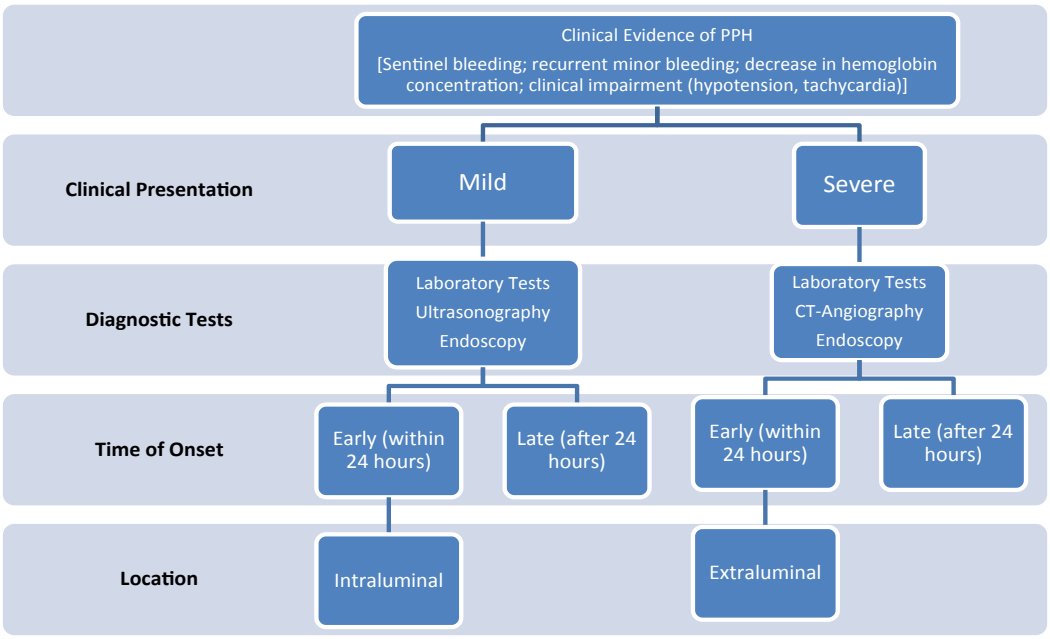

Figure 2. Diagnostic approach towards categorizing PPH.

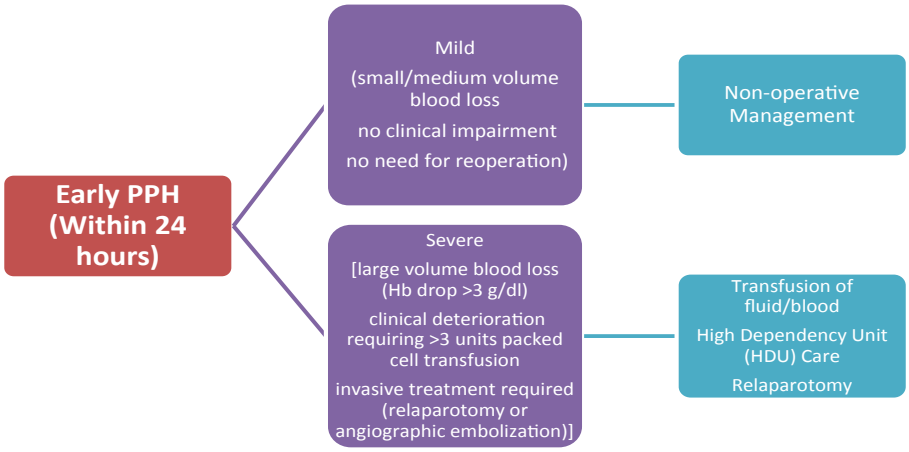

Figure 3. Management of early PPH [13, 28].

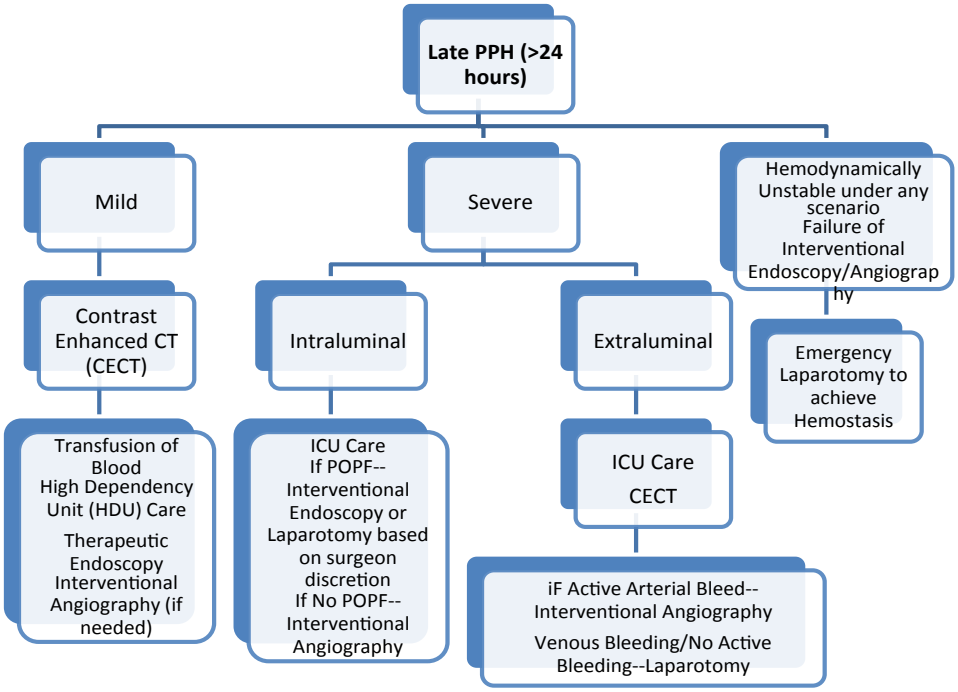

Figure 4. Management of late PPH [13, 16, 18, 28].

make this procedure even more difficult—for these reasons, interventional endoscopy/angiography is the preferred approach, upon failure of which laparotomy can be considered, albeit with a high mortality risk [29]. Mortality as high as 47% has been reported after operative procedures, against a mortality of 22% with radiological procedures, with the reported difference being statistically significant [18]. Compared to earlier cohorts up till 2009, studies from 2010 onwards have shown a decreasing trend of relaparotomy being performed as the initial procedure for late PPH, with a documented decrease of almost 7% over the years [27].

Yekebas et al. identified 2 major indications for surgical exploration in their series:

(1) Acute life-threatening hemodynamic instability with Hb drop ≥ 3 g/dl or evident blood drained *via* NGT or percutaneous drains.

(2) Critical hemodynamic deterioration requiring >6 units of PRBCs administration in 12 hours [19]. Surgical procedures adopted for PPH management range from simple suture ligation of the bleeding sites or vascular reconstruction to completion pancreatectomy, especially with coincident POPF. It appears; therefore, that relaparotomy with control of bleeding should be attempted primarily for severe early PPH, and should be reserved for late PPH only after failure of interventional procedures [28].

Interventional angiography: Angiography is the proposed intervention of choice for extraluminal PPH [18, 30], with the motive being avoidance of damage to sensitive anastomotic regions, as well as SIRS (systemic inflammatory response syndrome) [16]. In the series followed by Wellener et al. 50% success rate for interventional angiography in identification of bleeding site and hemostasis was reported [16]. Smaller, more recent series have reported a successful localization rate of 80% for angiography [17]. The relevance of angiography has increased over time, with an incidence of 24.6% from 2010-2014 compared against only 4.3% from 1994-2009 [27]. Cases of false-negative angiography are attributable to intermittent bleeding stops, or venous origin of bleeding [16, 31].

Angiographic procedures that can be performed include coil embolization or stenting: while the former is more commonly employed, the latter is of importance in situations where major visceral vessel occlusion is to be avoided while achieving hemostasis [16]. Stent grafting is associated with a risk of stent thrombosis, leading to liver abscesses and hepatic failure, which accounts for a higher case fatality rate [27]. In the absence of routine antiplatelet agent use, the rate for this risk is around 10% [32], which can be reduced by combined clopidogrel-aspirin therapy to inhibit platelet function. In contrast, coil embolization requires no antiplatelet therapy, and can be used as a salvage maneuver to prevent visceral arterial haemorrhage however, embolization of the main hepatic artery can cause liver ischemia in up to 83% of the patients, leading to a high case-fatality rate [27, 33]. Angiography should also be routinely employed for investigation and embolization of sentinel bleeds-even in emergency situations if required, because it can detect and manage pseudoaneurysms as well [34]. Although recommendations consider performing angiography for every sentinel bleed necessary, this is not currently the clinical practice in most centers [35].

Interventional endoscopy: Primary endoscopy is the option of choice for intraluminal bleeding diagnosed on CECT, with a variable reported success rate between 20 and 42% [36]. In the early postoperative period, endoscopy is generally not preferred, because of the risk of possible pancreatoenteric and bilioenteric anastomotic damage after GI insufflation [16, 19]. Endoscopy has also gained popularity over the decades, with an incidence of 30% from 2010-14 compared to only 7% before this period; however, evidence for its use is still conflicting. In many cases it is unable to localize the bleeding site [16, 24], leading some authors to believe it has poor results in delayed PPH [37].

One problematic presentation is pseudo-intraluminal bleeding, which is actually extraluminal, but presents as GI bleeding from the anastomotic site, often associated with presence of POPF. In such situations, interventional angiography or surgery is better suited to deal with the problem, and should be preferred over endoscopy [16].

Management strategies differ for early and late PPH, with early having a better therapeutic prognosis. **Figures 3 and 4** highlight a basic algorithm for clinical management of early and late PPH. These algorithms are based on clinical evidence from multi-centre studies and meta-analyses, and are applicable for PPH management in most high-volume as well as low volume centres.

Prevention of PPH

Prevention of PPH relies, to a large extent, on the early recognition and prompt management of the risk factors promoting PPH. Systematically, therefore, careful attention must be paid to seek and manage these factors in the pre-operative, intra-operative and post-operative phase. While no defined guidelines for prevention exist, several studies have linked certain measures to having a preventative effect in PPH. These include prompt management of intra-abdominal sepsis and pancreatic leaks-the mainstay preventive measures [18]; as well as certain operative measures, such as wrapping of the falciform ligament around the gastroduodenal artery stump [38]; or the use of round ligament of liver as a separator between the hepatic artery and pancreatic anastomosis [39]. Monitoring of perioperative antithrombotic use can also help reduce incidence of PPH [23]. Careful recognition of sentinel bleeding, with urgent angiography is also an effective measure for preventing late PPH. According to one series, uncinated process necrosis can also contribute to late PPH-removal of the uncinated process; therefore, can help in preventing hemorrhage from residual tissue [40]. Other methods, with substantially less clinical evidence, include

improving perioperative nutrition, reducing intraoperative transfusions, building better anastomoses, and preventing pancreatic leakage and intra-abdominal sepsis.

CONCLUSION

Post-pancreatectomy hemorrhage is a significant complication of pancreatic surgery, occurring in 5-12% of the cases. Late PPH is more common, accounting for a high morbidity and mortality. In clinical practice, the ISGPS classification should be used to categorize PPH, because of its significant relevance; however, attention should be made so as not to overlook grade-A hemorrhage. Sentinel bleeds herald the possibility of delayed PPH, and should be carefully monitored. CT-angiography should be used to evaluate all suspected or actual cases of PPH, and management should be planned according to proposed algorithms, with exploration given preference only in hemodynamically unstable patients or after failure of interventional methods. Interventional angiography is a novel method to deal with extraluminal and pseudo-intraluminal hemorrhage, and centers should make arrangements regarding its availability. Lastly, risk factor monitoring and reduction can help prevent the incidence of PPH, as well as the associated mortality.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

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