# Delayed Massive Hemorrhage After Pancreatic and Biliary Surgery

**Embolization or Surgery?** 

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**Results:** The incidence of DMH (SG 2.3% vs. HCG 3.2%) declined somewhat but did not differ significantly between both periods. The number of patients with a septic complication (SG 74% vs. HCG 50%) and a sentinel bleed (SG 78% vs. HCG 100%) before the onset of DMH did not differ significantly. Embolization (SG 2 of 2 patients vs. HCG 0 of 2 patients) was not used frequently. Successful outcome after surgical intervention (SG 14 of 16 patients vs. HCG 8 of 14 patients) and the surgical procedures performed to obtain hemostasis were comparable and overall mortality (SG 22% vs. HCG 29%) was comparable.

**Conclusions:** The incidence of DMH declined somewhat from 3.2% to 2.3% over the past years. Most patients present with septic complications and a sentinel bleed before onset of DMH. Despite general acceptance of embolization in our unit, it was used infrequently in patients with DMH. Aggressive surgical intervention was the treatment of choice in patients with DMH after pancreatic or biliary surgery.

(Ann Surg 2005;241: 85-91)

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DOI: 10.1097/01.sla.0000150169.22834.13

The mortality rate after major pancreatic and biliary surgery has decreased considerably over the past decade and is currently between 0% and 5%.<sup>1–5</sup> Despite progress, procedures such as pancreatoduodenectomy or hepatic resection for proximal bile duct malignancies are still associated with a morbidity rate of 30% to 40%.<sup>1–6</sup> The most common complications after pancreatoduodenectomy are delayed gastricemptying, pancreatic leakage, and intraabdominal abscess formation.<sup>7–9</sup> Bile leakage and abscess formation are the most common complications after resection of the proximal bile duct, whereas postoperative hepatic failure is most common if this procedure is combined with (extended) hepatic resection.<sup>5,10,11</sup>

Hemorrhage after major pancreatic or biliary surgery is a less common but dramatic complication that can occur in the early or late postoperative phase. Hemorrhage within the first 24 hours after surgery is generally caused by a technical failure and needs immediate adequate hemostasis through a relaparotomy. Usually, it is bleeding from a nonsecured vessel. Hemorrhage in the late postoperative phase may originate from the gastrointestinal tract such as peptic ulceration or ulceration from the anastomosis, but can also be from an intraabdominal site such as an eroded vessel or dehiscence of an anastomotic suture line. A late onset of hemorrhage has previously been described as delayed massive hemorrhage (DMH).<sup>12–15</sup>

Delayed massive hemorrhage generally presents as a sudden or intermittent massive intraabdominal hemorrhage; many others like ourselves advised surgical intervention.<sup>12–16</sup> Recent case reports and small series of successful arterial embolization for bleeding from pseudoaneurysms and general acceptance of this method in our institution for other indications prompted the question of whether this treatment has been used more frequently and in particular for these severe bleedings.<sup>17,18</sup>

The aim of our study was to analyze the incidence, presentation, diagnostic procedures, and management of

Annals of Surgery • Volume 241, Number 1, January 2005

**Objective:** To analyze the management of delayed massive hemorrhage (DMH) after major pancreatic and biliary surgery.

**Summary Background Data:** Despite a decreased mortality rate for pancreatic and biliary surgery, DMH is still an important cause of postoperative mortality. The aim of the present study was to analyze the management of DMH after pancreatic and biliary surgery, and specifically to assess the role of embolization and surgical intervention.

**Methods:** The study group (SG) consisted of 1010 patients from 1994 to 2002 who underwent pancreatic or biliary surgery (cholecystectomy excluded). Patients from a previous study (1983–1993, n = 686) were used as a historical control group (HCG).

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DMH after pancreatic and biliary surgery and to study a possible change by comparing the results with a historical control group.<sup>12</sup>

# MATERIALS AND METHODS

Patients were divided into 2 groups: the study group and the historical control group. The study group (SG) consisted of 1010 patients who underwent pancreatic or biliary surgery (cholecystectomy excluded) from 1994 to 2002. Inclusion criteria were a postoperative bleeding occurring 24 hours after the index operation and a transfusion need of at least 4 packed cells within 24 hours.

The historical control group (HCG) consisted of 686 patients and was previously described.<sup>12</sup> The inclusion criteria for the HCG were 6 or more packed cells with the same time standard. The number of packed cells used as inclusion criteria was lowered in the study group because of a stricter policy toward use of blood products during the past decade.

In both groups, the following surgical procedures were analyzed for DMH: (pylorus-preserving) pancreatoduodenectomy, (sub)total pancreatic resection, proximal bile duct resection with or without hemihepatectomy, bilidigestive anastomosis, and pancreaticojejunostomy for chronic pancreatitis with or without hepaticojejunostomy. Biliary T-drains or transhepatic biliary drainage was not used routinely. A drain through the jejunal loop was only used if the anastomosis was made at the proximal (segmental) branches of the hepatic duct and a transhepatic drain was left behind if placed preoperatively. One silicone drain (27 gauge) was placed near the anastomosis in all patients. After pancreatic resection, the drain is generally removed on the seventh postoperative day or earlier if production has stopped and the condition of the patient justifies removal. The drain is removed earlier after biliary reconstruction.

Specific parameters of patients with DMH analyzed include patient characteristics, symptoms and signs between index operation and DMH, bleeding characteristics, diagnostic workup, therapeutic interventions, and outcome.

Sepsis in the postoperative period was defined as either bacteremia (a body temperature of at least  $38.5^{\circ}$ C combined with a leukocyte count of  $15 \times 10^{9}$ /L or higher) or the presence of intraabdominal abscesses or anastomotic leakage. Anastomotic leakage was defined as a high amylase level in the abdominal drains (>3-time serum amylase), bile contents in the abdominal drains or leakage found at relaparotomy. Hemodynamic instability was defined as a mean arterial pressure lower than 70 mm Hg (normal range, 70–110 mm Hg) before resuscitation with intravenous fluids or the administration of blood products. A sentinel bleed was defined as any kind of minor symptomatic hemorrhage requiring no intervention and occurring 24 hours after the index operation and before onset of DMH. Bleedings of patients who met the inclusion criteria were divided into septic, arterial, or gastrointestinal suture-line bleedings. Septic bleedings were defined as DMH in any patient who had a septic episode (as described previously) before onset of DMH. Diagnostic procedures were analyzed regarding the success rate in detecting DMH and comprised gastrointestinal endoscopy, erythrocyte scanning, angiography, ultrasonography, and computed tomography. Ultrasonography and computed tomography played a supplementary role in detecting abscesses or local inflammatory processes.

All therapeutic interventions performed were analyzed regarding success rate in controlling the bleedings. Conservative measures consisted of supportive therapy, including gastric drainage, antibiotics, blood products, and supportive drugs (eg, somatostatin for patients undergoing pancreatic surgery). Sclerotherapy was performed using adrenaline 0.01% or ethoxysclerol 1%. During angiography, both the celiac trunk (including the hepatic and splenic artery) as well as the superior mesenteric artery was visualized. Embolization was performed by coil occlusion or placement of a covered stent.

Surgical interventions were reviewed and divided according to the type of surgery performed. Generally, exploration and ligation of the bleeding vessel and removal of the intraabdominal hematoma was performed, with reconstruction of the anastomosis if possible.

Finally, a separate analysis was performed of all variables for septic, arterial, and suture-line bleedings per group.

Statistical analysis was performed using the chisquared test, the 2-tailed Fisher exact test, and the Mann-Whitney U analysis, when applicable. A P value below 0.05 was considered significant.

## RESULTS

In the study group in the period 1994 to 2002, 1010 patients underwent major pancreatic and biliary surgery (Table 1). Delayed massive hemorrhage occurred in 23 of these patients (2.3%) after major pancreatic or biliary surgery compared with 22 patients (3.2%) in the control group (Table 1). The incidence of DMH after the different surgical procedures was not significantly different for both groups. The incidence of DMH after bilidigestive surgery was lower (SG 0.5% vs. HCG 2.2%, P = 0.11).

# Characteristics and Location of Patients With Delayed Massive Hemorrhage

There were no significant differences in age, gender, or pathology between both groups (Table 2). The incidence of septic complications before the onset of DMH (SG 74% vs. HCG 50%, P = 0.1) was higher and the incidence of anastomotic leakage (SG 65% vs. HCG 23%, P < 0.01) was significantly higher. The incidence of sentinel bleedings (SG 78% vs. HCG 100%, P = 0.05) was slightly lower. Hematemesis (SG 10 patients vs. HCG 14 patients) occurred most

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	Study Group* (1994–2002)			Historical Control Group <sup>†</sup> (1983–1993)			<b>Total</b> (1983–2002)		
	Total D		DMH	Total	]	DMH		DMH	
Resection									
Pancreatoduodenectomy	399	11	(2.8%)	208	6	(2.9%)	607	17	(2.8%)
(Sub)total pancreatic resection	43	1	(2.3%)	93	1	(1.1%)	136	2	(1.5%)
Proximal bile duct resection	73	4	(5.5%)	104	8	(7.7%)	177	12	(6.8%)
Bypass									
Bilidigestive anastomosis	382	2	(0.5%)	230	5	(2.2%)	612	7	(1.1%)
Panceaticojejunal anastomosis	113	5	(4.4%)	51	2	(3.9%)	164	7	(4.3%)
Total	1010	23	(2.3%)	686	22	(3.2%)	1696	45	(2.7%)

packed cells within 24 h and more than 24 h after index operation.

 $^{\dagger} \ge 6$  packed cells within 24 h and more than 24 h after index operation.

TABLE 2. Characteristics of Patients With Delayed Massive Hemorrhage (DMH)

	Study Group*	Historical Control Group <sup>†</sup>
	(n = 23)	(n = 22)
Patient characteristics		
Mean age (range)	57 (33-81)	55 (42-72)
Gender (male/female)	15/8	16/6
Pathology of index operation		
Pancreatic head/periampullary cancer	11	11
Chronic pancreatitis	5	3
Proximal bile duct tumor	5	5
Benign tumor	2	3
No. of patients with sepsis in postoperative phase before DMH	17 (74%)	11 (50%)
Bacteremia	11	10
Abscesses	9	10
No. of patients with anastomotic leakage before DMH	15 (65%) <sup>‡</sup>	5 (23%) <sup>‡</sup>
Pancreaticojejunostomy	9	4
Hepaticojejunostomy	7	2
Gastroenterostomy	3	0
No. of patients with sentinel bleeding before DMH	18 (78%)	22 (100%)
Bleed from abdominal drain	9	8
Melena	8	13
Hematemesis	10	14
Blood loss per anum	6	_
No. of patients who underwent relaparotomy before DMH	7 (30%)	3 (14%)

 $*\geq$ 4 packed cells within 24 h and more than 24 h after index operation.  $^{\dagger}\geq 6$  packed cells within 24 h and more than 24 h after index operation. P < 0.05

Missing data (---) for historical control group.

often, followed by melena (SG 8 patients vs. HCG 13 patients) or a bleeding from the abdominal drains (SG 9 patients vs. HCG 8 patients). The number of patients who underwent relaparotomy was higher (SG 35% vs. HCG 14%, P = 0.28).

The mean postoperative interval in days between surgery and DMH (SG 17.6  $\pm$  14.8 vs. HCG 11.0  $\pm$  13.1, P = 0.12) was longer (Table 3). The mean hemoglobin level before the administration of blood products (SG  $3.9 \pm 0.9$  vs. HCG 4.7  $\pm$  1.1, P = 0.01) was significantly lower. The number of patients with hemodynamic instability before transfusion (SG 44% vs. HCG 41%, P = 0.86) was comparable. The number of units of packed cells transfused (SG  $8.9 \pm 4.3$  vs. HCG 13.7  $\pm 6.7$ , P < 0.01) was significantly lower.

Most patients had septic DMH (SG 74% vs. HCG 50%, P = 0.1). An arterial DMH (SG 17% vs. HCG 9%, P = 0.67) occurred more often and a gastrointestinal suture-line DMH (SG 9% vs. HCG 41%, P = 0.01) occurred significantly less often. Bleeding from the hepatic artery (SG 1 patient vs. HCG 6 patients, P = 0.05) occurred less often and from the gastroenterostomy (SG 1 patient vs. HCG 7 patients, P =0.02) occurred significantly less often.

## **Diagnostic Procedures**

Successful detection of DMH by gastrointestinal endoscopy (SG 4 of 10 vs. HCG 7 of 11, P = 0.4) was lower (Table 4). Radionuclide erythrocyte scan was rarely successful (SG 0 of 1 vs. HCG 1 of 4, P = 0.58) in detecting DMH. Successful detection of DMH by angiography (SG 4 of 8 vs. HCG 4 of 9, P = 0.82) was comparable. Ultrasonography and computed tomography was analyzed in the study group for successful detection of abscesses or local inflammatory processes in patients with bacteremia and successful detection was seen in 9 of 13 and 9 of 11 patients, respectively.

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	Study Group*	Historical Control Group <sup>†</sup>
	(n = 23)	(n = 22)
Postoperative interval in days, mean (SD)	17.6 (14.8)	11.0 (13.1)
Hemoglobin before transfusion in mmol/L, mean (SD)	3.9 (0.9) <sup>‡</sup>	4.7 (1.1) <sup>‡</sup>
No. of hemodynamic unstable patients before transfusion	10 (40%)	9 (41%)
Units PC within 24 h, mean (SD)	8.9 (4.3) <sup>‡</sup>	13.7 (6.7) <sup>‡</sup>
Septic DMH	17 (74%)	11 (50%)
Gastroduodenal artery	4	2
Artery in mesentery	1	0
Hepatic artery	1	6
Artery in pancreatic parenchyma	1	0
Pancreaticojejunostomy	5	2
Gastroenterostomy	0	1
Enteroenterostomy	1	0
Hepaticojejunostomy	4	0
Arterial DMH	4 (17%)	2 (9%)
Artery in pancreatic parenchyma	1	0
Splenic artery	2	1
Hepatic artery	1	1
Suture-line DMH	2 (9%)‡	9 (41%) <sup>‡</sup>
Gastroenterostomy	1‡	7‡
Enteroenterostomy	0	2
Pancreaticojejunostomy	1	0

**TABLE 3.** Characteristics of Delayed Massive Hemorrhage (DMH) and Location of Septic, Arterial, and Suture-Line Bleeding

\* $\geq$ 4 packed cells within 24 h and more than 24 h after index operation. † $\geq$ 6 packed cells within 24 h and more than 24 h after index operation. ‡P < 0.05. SD indicates standard deviation.

Management and Outcome

Conservative measures (SG 5 patients vs. HCG 0 patients, P = 0.05) were performed more often and successful in 2 patients; all patients received blood transfusions and antibiotics; patients who underwent pancreatic surgery received octreotide analogs (100  $\mu$ g subcutaneously) for 5 days or longer (Table 5). One patient died of bleeding on the way to the operating room and 2 died of fulminant sepsis after the bleeding was controlled conservatively. One of these last patients had a pancreatic head adenocarcinoma with distant metastasis and refused invasive treatment and the other patient had a too-poor condition for surgery as a result of sepsis.

Radiologic embolization was performed twice in both groups during diagnostic angiography. The procedure was successful in both patients in the study group compared with

#### TABLE 4. Diagnostic Procedures

	Study Group*	Historical Control Group <sup>†</sup>
	(n = 23)	(n = 22)
Delayed massive hemorrhage		
Gastrointestinal endoscopy <sup>‡</sup>	4/10	7/11
Erythrocyte scan <sup>‡</sup>	0/1	1/4
Angiography <sup>‡</sup>	4/8	4/9
Intraabdominal inflammation		
Ultrasonography <sup>‡</sup>	9/13	
Computed tomography <sup>‡</sup>	9/11	
*≥4 packed cells within 24 h at <sup>†</sup> ≥6 packed cells within 24 h at <sup>‡</sup> No. successful/no. performed.		1

Missing data (—) for historical control group.

none in the control group. One patient had a bleeding pseudoaneurysm from a branch of the hepatic artery (Fig. 1) and 1 had bleeding from the gastroduodenal artery. The 4 other patients with positive diagnostic angiography had too small bleedings for embolization.

Outcome after surgical intervention (SG 14 of 16 patients vs. HCG 14 of 18 patients, P = 0.34) and the surgical procedures performed to obtain hemostasis were comparable. Five deaths were the result of fulminant sepsis during the recovery period after successful hemostasis. No deaths were directly related to bleeding in the study group, and 1 patient in the control group died because of uncontrollable bleeding after a negative exploratory laparotomy.

The mean arterial pressure before transfusion was slightly higher in patients who underwent embolization compared with patients who underwent surgery (79  $\pm$  21.3 mm Hg vs. 70  $\pm$  12.7 mm Hg, P = 0.296, respectively).

Overall, death resulting from uncontrollable bleeding occurred in 1 patient in each group. All other patients died of fulminant sepsis as a result of leakage of the hepaticojejunostomy (n = 4), leakage from the pancreaticojejunostomy (n = 2), multiple organ failure (n = 2), and multiple liver abscesses (n = 1). The overall mortality (SG 22% vs. HCG 27%, P = 0.67) was comparable for both groups.

Delayed massive hemorrhage had a longer postoperative interval for patients with septic bleedings compared with patients who had arterial or suture-line bleedings (Table 6). All relaparotomies before onset of DMH were performed in patients with septic bleedings, and all mortality occurred in patients with a septic bleeding. The differences were not statistically significant.

# DISCUSSION

In this series, the incidence, presenting symptoms, diagnostic procedures, and management of DMH after pan-

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	Study Group*	Historical Control Group <sup>†</sup>		
	(n = 23)	(n = 22)		
Conservative <sup>‡</sup>	2/5	0		
Embolization <sup>‡</sup>	2/2	0/2		
Sclerotherapy <sup>‡</sup>	0	2/2		
Surgical hemostasis <sup>‡</sup>	14/16	14/18		
Anastomotic resection and reconstruction <sup>‡</sup>	2/3	4/4		
Vessel ligation <sup>‡</sup>	8/8	10/13		
Completion pancreatectomy <sup>‡</sup>	4/4	0		
Exploration <sup>‡</sup>	0/1	0/1		
Overall mortality	5 (22%)	6 (27%)		
Mortality as a result of uncontrollable bleeding	1	1		
Mortality as a result of fulminant sepsis	4	5		

\*≥4 packed cells within 24 h and more than 24 h after index operation.  $^{\dagger} \ge 6$  packed cells within 24 h and more than 24 h after index operation. <sup>‡</sup>No. successful/no. performed

creatic and biliary surgery were analyzed. We found that the incidence of DMH has declined only a little over the years, and that most patients had a septic complication and presented with a sentinel bleed before onset of DMH. We also found that ultrasonography and computed tomography play a supplementary role in detecting intraabdominal inflammation and that embolization has not been used frequently. Surgical intervention is still the most successful treatment, and fulminant sepsis was the main cause of death in the patients who died.

Different pathophysiological mechanisms have been suggested for DMH. First, erosion of arterial vessels resulting from intraabdominal contamination of enteric, pancreatic, and/or bile juice from a leaking anastomosis can cause DMH.<sup>19</sup> The erosive properties of these juices are thought to be directly responsible for DMH. Dissected vessels submitted to intraoperative injury to the vascular wall during extensive lymphatic dissection could also make vessels more vulnerable to the erosive juices.<sup>20</sup> Cullen et al, in a study of 66 patients, reported intraabdominal hemorrhage in 12% of the patients with anastomotic leakage, whereas no hemorrhage occurred in patients without leakage.<sup>21</sup> The authors also showed a positive correlation between intraabdominal hemorrhage and leakage-related mortality as was the case in the present series.

A second possible mechanism might be local infection and abscess formation in the intraabdominal cavity.<sup>19</sup> This

FIGURE 1. (A) Hemorrhage originating from a false aneurysm of the common hepatic artery after pancreatoduodenectomy.

inflammatory process may also lead to arterial erosion or could result in dehiscence of the anastomosis with bleeding from the exposed suture line.<sup>19</sup> These suture-line bleeds have been reported as being very serious and require transfusions similar to those indicated for intraabdominal arterial hemorrhage.12

Finally, pancreatic leakage may lead to formation of a pseudocyst. If pancreatic enzymes from a pseudocyst erode into an adjacent arterial vessel, the vessel can become eroded in such a way that blood flows into the cyst, producing a pseudoaneurysm, which in turn can rupture and lead to DMH.<sup>22,23</sup>

Encouraging results have been reported after arterial embolization, being a safe and minimally invasive procedure to obtain hemostasis in patients with pseudoaneurysms with a success rate reported between 63% and 79%.14,17,18,23,24 When considering embolization for DMH after pancreatic or

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(B) Covered stent successfully placed over the false aneurysm (black arrows).

	Study Group*			Historical Control Group $^{\dagger}$			
		(n = 23)			(n = 22)		
	Septic	Arterial	Suture-Line	Septic	Arterial	Suture-Line	
	(n = 17)	(n = 4)	(n = 2)	(n = 11)	(n = 2)	(n = 9)	
Postoperative interval in days, mean (SD)	20.8 (14.9)	10.8 (13.6)	4.5 (3.5)	15.3 (16.5)	15.5 (6.4)	3.9 (2.1)	
Units of packed cells within 24 h, mean (SD)	8.4 (3.9)	12.3 (4.9)	5.0 (0)	14.6 (6.0)	21.0 (15.6)	10.9 (4.2)	
No. of patients who underwent relaparotomy before DMH	7 (41%)	0	0	3 (27%)	0	0	
Mortality	5 (29%)	0	0	6 (55%)	0	0	

TABLE 6. Septic, Arterial, and Suture-Line Delayed Massive Hemorrhage (DMH) per Group

\* $\geq$ 4 packed cells within 24 h and more than 24 h after index operation.

 $^{\dagger}\geq 6$  packed cells within 24 h and more than 24 h after index operation.

SD indicates standard deviation.

biliary surgery, a few factors have to be taken into account. First, like in the present series, not all cases of DMH were caused by ruptured pseudoaneurysms. Another more frequently reported problem also seen in the present series is the limited detection rate of angiography as a result of the intermittent pattern of the bleedings.<sup>13,17</sup> Finally, most patients in the present series have concomitant septic complications and are initially managed in the intensive-care unit. The selection of the final management is partly dependent on resuscitation facilities at the department of radiology. In the acute situation (especially at night or on weekends), physicians on call are generally reluctant to transport a hemodynamically unstable patient to the radiology department without standard equipment for resuscitation and intubation. Therefore, there might be a bias that patients who were already in severe shock or otherwise had septic complications underwent surgery more frequently. Ideally, interventional radiologic facilities in the operating room with adequate support of anesthesiologists and optimal resuscitation would promote the use of embolization as primary stabilizing therapy because surgery can be performed as a next step in the same location.<sup>13,17</sup>

The present series consisted mostly of patients with severe sepsis resulting from anastomotic leakage. Some patients underwent surgical intervention before the onset of DMH. However, most patients were initially managed conservatively in the intensive-care unit, and DMH was the event that prompted the surgeon to perform an emergency laparotomy.

The importance of the sentinel bleed has been recognized by several authors.<sup>13,15,17</sup> Meticulous analysis of our records of the 388 patient who underwent pancreatoduodenectomy and did not develop DMH showed that 4 patients had a sentinel bleed that was not followed by DMH. However, none of these 4 patients had septic complications in the postoperative phase.

A more conservative attitude toward the transfusion policy of blood products when confronted with hemorrhage made us decide to lower the inclusion criteria to 4 packed cells within 24 hours. The hemoglobin level at which to administer packed cells is also lower in the study group as compared with the historical controls. This may be a consequence of a more reserved use of blood products. Comparison with other studies is thus almost impossible as a result of widely differing definitions of DMH. This is also partly the problem when comparing the groups in the present series.

Delayed massive hemorrhage after pancreatic or biliary surgery is a severe complication and carries a high mortality rate. Postoperative sepsis should be observed with great care, and if a sentinel bleeding presents, the surgeon should seriously consider the possibility of imminent DMH and perform an emergency angiography. If embolization fails, the management of DMH is still aggressive surgery.

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