Impact of medical complications on outcome after subarachnoid hemorrhage*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify common medical complications after subarachnoid hemorrhage.
2. Describe complications that influence outcome.
3. Use this inofrmation in a clinical setting.

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Objective: **Medical complications occur frequently after subarachnoid hemorrhage (SAH). Their impact on outcome remains poorly defined.**

Design: **Inception cohort study.**

Patients: **Five-hundred eighty patients enrolled in the Columbia University SAH Outcomes Project between July 1996 and May 2002.**

Setting: **Neurologic intensive care unit.**

Interventions: **Patients were treated according to standard management protocols.**

Measurements and Main Results: **Poor outcome was defined as death or severe disability (modified Rankin score, 4–6) at 3 months. We calculated the frequency of medical complications according to prespecified criteria and evaluated their impact on outcome, using forward stepwise multiple logistic regression after adjusting for known predictors of poor outcome. Thirty-eight% had a poor outcome; mortality was 21%. The most frequent complications were temperature >38.3°C (54%), followed by anemia treated with transfusion (36%), hyperglycemia >11.1 mmol/L (30%), treated hypertension (>160 mm Hg systolic; 27%), hypernatremia >150 mmol/L (22%), pneumonia (20%), hypotension (<90 mm Hg systolic) treated with vasopressors (18%), pulmonary edema (14%), and hyponatremia <130 mmol/L (14%). Fever (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.1–3.4; $p = .02$), anemia (OR, 1.8; 95% CI, 1.1–2.9; $p = .02$), and hyperglycemia (OR, 1.8; 95% CI, 1.1–3.0; $p = .02$) significantly predicted poor outcome after adjustment for age, Hunt-Hess grade, aneurysm size, rebleeding, and cerebral infarction due to vasospasm.**

Conclusions: **Fever, anemia, and hyperglycemia affect 30% to 54% of patients with SAH and are significantly associated with mortality and poor functional outcome. Critical care strategies directed at maintaining normothermia, normoglycemia, and prevention of anemia may improve outcome after SAH. (Crit Care Med 2006; 34:617–623)**

KEY WORDS: subarachnoid hemorrhage; medical complications; fever; anemia; hyperglycemia; outcome

Aneurysmal subarachnoid hemorrhage (SAH) is a potentially devastating illness with a high mortality rate (1–5). The most important independent determinants of outcome after SAH include neurologic state on presentation (3, 6–11), age (6, 8, 10–12), large aneurysm size (>10 mm) (9), and aneurysm rebleeding (13–15). Delayed cerebral ischemia from vasospasm has also been consistently associated with poor neurologic outcome and mortality (14, 16, 17).

In addition to the direct effects of the initial hemorrhage and secondary neurologic complications, SAH also predisposes to medical complications that may have an impact on outcome. In the placebo group of the Cooperative Aneurysm Study investigating the effects of nicardipine, the most frequent nonneurologic complications were identified as anemia, hypertension, cardiac arrhythmia, fever, and electrolyte abnormalities. The proportion of deaths directly attributable to

***See also p. 897.**

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Table 1. Medical complications after subarachnoid hemorrhage and their impact on outcome

Complication	Definition	No. (%) Affected (n = 576)	Odds Ratio (95% Confidence Interval) for Poor Outcome	*p* Value
Fever	Temperature >38.3 °C	309 (54)	4.4 (3.0–6.4)	<.0001
Anemia	Hemoglobin <1.4 mmol/L (9 mg/dL) treated with transfusion	206 (36)	2.5 (1.8–3.6)	<.0001
Hyperglycemia	Serum glucose >11.1 mmol/L (200 mg/dL)	174 (30)	4.2 (2.9–6.1)	<.0001
Hypertension[a]	Systolic BP >160 mm Hg treated with continuous IV medication	156 (27)	2.1 (1.4–3.0)	<.0001
Hypernatremia[b]	Serum sodium >150 mmol/L	91 (22)	8.1 (4.6–14.1)	<.0001
Pneumonia	New infiltrate on CXR with fever or purulent sputum	114 (20)	4.3 (2.8–6.6)	<.0001
Hypotension	Systolic BP <100 mm Hg treated with vasopressors	105 (18)	7.1 (4.4–11.6)	<.0001
Pulmonary edema	Increased Aa gradient, pulmonary edema on CXR	82 (14)	4.2 (2.5–6.9)	<.0001
Hyponatremia	Serum sodium <130 mmol/L	81 (14)	—	.19
Urinary tract infection	Urine white cell count >5/hpf and positive urine culture	77 (13)	1.7 (1.1–2.8)	.025
Delirium	Acute onset of fluctuating confusion, agitation, inattention	53 (9)	—	.356
Bloodstream infection	Positive blood cultures with local IV erythema or SIRS	48 (8)	2.7 (1.5–5.0)	.001
Arrhythmia	Life-threatening cardiac arrhythmia confirmed by ECG	46 (8)	6.0 (3.0–12.0)	<.0001
Myocardial ischemia	Elevation of troponin I or CK-MB and ischemic ECG changes	35 (6)	6.2 (2.8–13.9)	<.0001
Seizures	Clinical or EEG ictal activity	31 (5)	6.2 (2.6–14.7)	<.0001
Meningitis/ventriculitis	Increased CSF white cell count and positive CSF culture	28 (5)	3.1 (1.4–6.9)	.003
Deep vein thrombosis[b]	Diagnosis by Doppler ultrasonography	23 (4)	3.2 (1.3–7.7)	.006
Gastrointestinal bleeding[b]	Hematochezia and hemoglobin <1.4 mmol/L (9 mg/dL) treated with transfusion	23 (4)	4.9 (1.9–12.7)	<.0001
Diabetes insipidus[b]	Increased urine output with urine SG <1.005 and hypernatremia	23 (4)	39.9 (5.3–298.6)	<.0001
Survived cardiac arrest[a]	Survival after in-hospital cardiopulmonary resuscitation	21 (4)	61.6 (8.2–463.9)	<.001
Allergic reaction[b]	Erythema, hives, or bronchospasm with improvement after exposure is eliminated	18 (3)	—	.93
Hepatic failure[b]	AST or ALT >200 U/L	17 (3)	5.6 (1.8–17.3)	.001
Renal failure[b]	Creatinine >221 μmol/L (2.5 mg/dL)	17 (3)	4.1 (1.4–11.8)	.005
Pneumothorax[b]	Diagnosis by CXR	15 (3)	4.7 (1.5–14.9)	.004
Wound infection[b]	Fever and presence of purulent wound discharge	7 (1)	—	.065
Pulmonary embolism[b]	Positive ventilation/perfusion scan or chest CT angiography	2 (0.3)	—	.069

BP, blood pressure; CXR, chest radiograph; Aa-gradient, alveolar-arterial partial pressure of oxygen gradient; IV, intravenous; SIRS, systemic inflammatory response syndrome; ECG, electrocardiogram; CK-MB, MB fraction of creatinine kinase; EEG, electroencephalogram; CSF, cerebrospinal fluid; SG, specific gravity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CT, computed tomography.

[a]Does not include pharmacologically induced hypertension for the treatment of symptomatic vasospasm; [b]medical complications that were excluded from the final multivariate model because of their low frequency (<5%) or their close association with treatment for a specific neurologic complication. Data are shown as number (%) for dichotomized variables. Chi-square test was used to calculate *p* values, odds ratios, and 95% confidence intervals in a univariate analysis. Complications were classified as present if they occurred at least once during hospitalization.

medical complications (23%) was comparable to that of vasospasm (23%) and rebleeding (22%) (18). However, the Cooperative Aneurysm Study excluded poor-grade patients, did not evaluate functional outcome, and did not control for the effect of established demographic and disease-related predictors of poor outcome.

In this study, we sought to determine the frequency of medical complications after SAH and to identify complications that significantly contribute to poor outcome.

MATERIALS AND METHODS

Patient Population. Five-hundred eighty patients with SAH admitted to the Columbia University Medical Center Neurologic Intensive Care Unit (NICU) between July 1996 and May 2002 were enrolled in the Columbia University SAH Outcomes Project. The study was approved by the hospital's institutional review board, and in all cases written informed consent was obtained from the patient or a surrogate. The diagnosis of SAH was established by computed tomography (CT) on admission or by xanthochromia of the cerebrospinal fluid if the CT scan was not diagnostic. Patients with aneurysmal and spontaneous nonaneurysmal SAH were included; patients <18 yrs old and those with SAH from trauma, arteriovenous malformations, or other secondary causes were excluded.

Clinical Management. The NICU management of patients with SAH has been described in detail previously (1, 9, 17). All patients received 0.9% normal saline at a dosage of 1 mL/kg/hr, and supplemental 5% albumin solution was administered to maintain central venous pressure at >5 mm Hg. Patients experiencing symptomatic cerebral ischemia received hypertensive hypervolemic therapy (HHT), involving a target central venous pressure of >8 mm Hg, induced hypertension with phenylephrine or norepinephrine to maintain systolic blood pressure 180–220 mm Hg, and maintenance of cardiac index at >4.0 L/min/m^2 with milrinone or dobutamine as needed. Intracranial hypertension and acute symptomatic intracranial mass effect were treated with repeated boluses of 20% mannitol (0.25–1.5 g/kg) or 23.4% hypertonic saline (0.5–2.0 mL/kg). In patients with persistent mass effect related to cerebral edema, 3% sodium-acetate solution was given to maintain serum osmolality at 320 mosm/L. Persistent fever (temperature exceeding 38.3°C) was treated with acetaminophen and external cooling blankets. Blood transfusions were given to maintain hemoglobin at >1.3 mmol/L (8 mg/dL), except in the presence of ongoing cerebral or cardiac ischemia, in which case a target hemoglobin of >1.6 mmol/L (10.0 mg/dL) was maintained. Persistent hyperglycemia exceeding 9.9 mmol/L (180 mg/dL) was treated with subcutaneous sliding-scale insulin every 4–6 hrs. Insulin infusion protocols were not routinely utilized unless glucose levels consis-

Table 2. Baseline features of the study population (n = 576)

Feature	Value
Age (yrs)	53 (16–89)
Females	392 (68)
Ethnicity	
Caucasian	293 (51)
Hispanic	156 (27)
African-American	89 (15)
Asian	29 (5)
Other	9 (2)
Identified aneurysm	513 (89)
Treatment of the aneurysm	
Clipping	310/513 (60)
Embolization	95/513 (19)
Untreated	108/513 (21)
Aneurysm Size >10 mm	116 (23)
Hunt and Hess Grade	
I: Mild headache	160 (28)
II: Severe headache ± cranial nerve palsy	80 (14)
III: Drowsy or mild focal deficit	178 (31)
IV: Stuporous	84 (15)
V: Deep coma	74 (13)
Rebleeding	58 (10)
Infarct due to vasospasm	77 (14)

Data are shown as number (%) for dichotomized variables and median (range) for abnormally distributed continuous variables.

tently exceeded 13.3 mmol/L (240 mg/dL) or ketosis developed.

Clinical Data. Demographic data (age, sex, and ethnicity), social history (tobacco, cocaine, and alcohol use) and medical history were obtained through patient and family interviews on admission. A general medical and neurologic evaluation was performed by a study neurointensivist on admission. Neurologic and medical status at onset was assessed with the Glasgow Coma Scale (GCS) (19), the Hunt Hess Scale (20), the National Institutes of Health Stroke Scale (NIHSS) (21), and the Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) Scale (22). An admission physiologic derangement score was calculated by subtracting the GCS, age, and chronic health elements from the APACHE-2 score (1). Admission and follow-up CT scans were independently evaluated by a study neurointensivist for the amount and location of blood (23), the presence of focal or global cerebral edema (9) and hydrocephalus (24), or infarction (17). Neurologic complications were defined as previously described (1, 9, 17). The definitions of medical complications are listed in Table 1; each complication was coded as present if it occurred at least once during the course of hospitalization. All complications were adjudicated by consensus of the entire study team in a weekly meeting. In this study we did not include neurogenic stunned myocardium in myocardial ischemia or infarction.

Outcome Assessment. Survival and functional outcome at 3 months were assessed with the modified Rankin Scale (mRS), a 7-point scale that grades neurologic outcome from death to full recovery without symptoms (25). When 3-month outcome was not available we used the 14-day assessment according to the principle of last observation carried forward. Poor outcome was defined as an mRS score of 4 to 6, indicating a state of moderate to severe disability (unable to walk), severe disability (bed-bound), or death. We selected this combined end point of death and moderate to severe disability to control for decisions to withdraw life support and because of uncertainty about patient preferences regarding the desirability of death vs. severe disability.

Statistical Analysis. Data analyses were performed with commercially available statistical software (11.0, SPSS, Chicago, IL). Univariate associations between predictor variables and poor outcome were tested with chi-square or Fisher's exact test for categorical variables, two-tailed *t*-test for normally distributed continuous variables, and Mann-Whitney U test for nonnormally distributed continuous variables. Among similar clinical variables that were intercorrelated, only the variable with the highest odds ratio (OR) and smallest *p* value in the binary logistic regression analysis was used as a candidate variable in the final multivariate model.

Significant predictors of poor outcome among the medical complications were identified in a forward stepwise logistic regression model with variables entered in order of their frequency of occurrence, after adjusting for known predictors of poor outcome in our dataset (older age, higher Hunt and Hess scale score, aneurysm size >10 mm, cerebral infarction due to vasospasm, and rebleeding) (9). Medical complications that occurred at a frequency of <5% or that resulted almost exclusively from treatment of neurologic complications (e.g., hypernatremia related to osmotherapy for cerebral edema) were excluded from the final model. Pearson product-moment correlation was used to assess the degree of intercorrelation between the significant medical complications identified in the final model.

We also tested for interactions between all independent predictors of outcome in the final model and whether year of admission or treatment modality (i.e., clipping vs. coiling) influenced outcome, by adding these variables individually to the final model. To determine the relative contributions of the individual predictors of poor outcome, we compared reductions in the Nagelkerke R^2 value of the entire model (an estimation of the overall fitness of the model) after individual removal of each significant predictor. *P* values <.05 were considered significant.

RESULTS

Demographic, Clinical, and Radiologic Characteristics. Outcome data were not available for four of the 580 patients, leaving 576 subjects for analysis. Baseline features of the study population are listed in Table 2. An aneurysm was identified in 513 patients, 21% (108) of whom were not treated because of poor grade, medical comorbidity, or anatomical considerations.

Frequency of Medical Complications. Seventy-nine percent of the study population (454/576) developed at least one medical complication during their hospitalization, and 55% (314/576) experienced two or more complications. The proportion of patients who experienced at least one medical complication was lower among those with a good 3-month outcome (69%; 244/356) than among those with a poor outcome (95%; 210/220; $p <$ .0001). Patients with poor 3-month outcome had significantly more medical complications (4.2 ± 3.4) than patients with good outcome (1.8 ± 2.2; $p <$ .0001).

Fever was the most frequent medical complication (54%), followed by anemia (36%), hyperglycemia (30%), and hypertension (27%) (Table 1, Fig. 1). Hypernatremia (>150 mmol/L) occurred at a frequency of 22% and was highly associated with osmolar therapy for intracranial hypertension or local mass effect; compared with other patients, those with hypernatremia more often had CT evidence of cerebral edema (76% vs. 30%; $p <$ .001), had clinical brain stem herniation (68% vs. 27%; $p <$ .001), and received mannitol (57% vs. 13%; $p <$ .001) and hypertonic saline (69% vs. 15%; $p <$ .001).

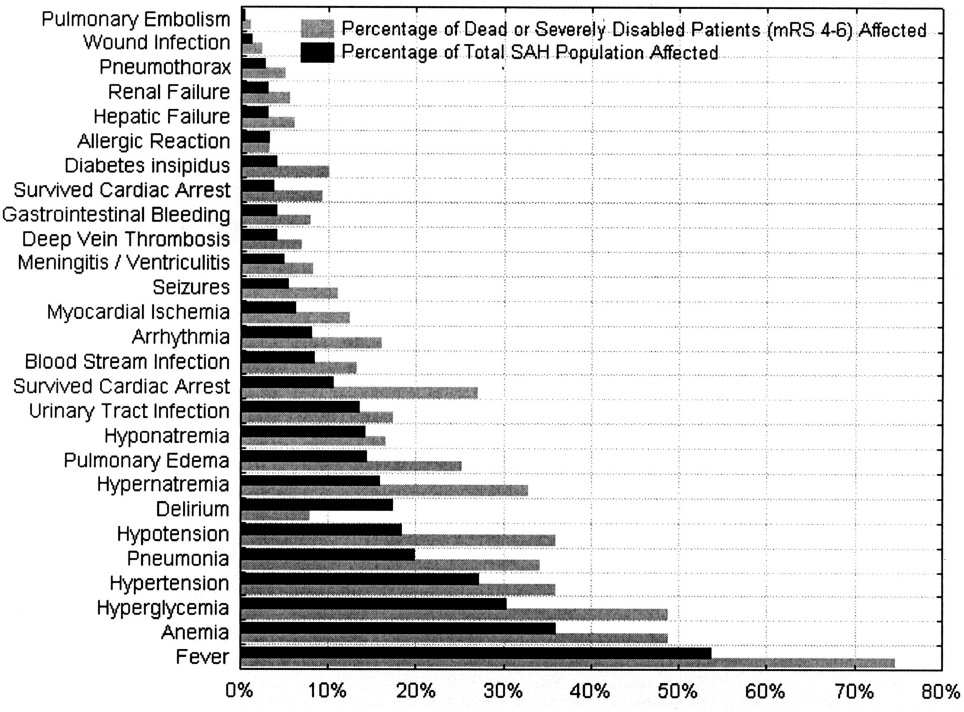

Figure 1. Percentage of medical complications in the study population of patients with subarachnoid hemorrhage (*SAH*) and among patients with poor outcome (modified Rankin Scale [*mRS*] score, 4–6) at 3 months.

Predictors of Poor Outcome. Mortality was 21% (119/576) 3 months after SAH, and 19% (111/576) were classified as mRS score 4 or 5. Ventilatory support was withheld or withdrawn from 8% of patients (48/576), and all of these patients died. Twenty complications were associated with poor outcome in the univariate analysis (Table 1). Forward stepwise logistic regression adjusted for known clinical predictors of poor outcome (older age, higher Hunt and Hess scale score, aneurysm size >10 mm, cerebral infarction due to vasospasm, rebleeding) (9) identified fever, anemia, and hyperglycemia as significant predictors of death or severe disability at 3 months (Table 3; $p < .05$ for the entire model). None of the remaining medical complications was significantly predictive when added to this model, nor was year of admission to the NICU or treatment modality (clipping vs. coiling). There were no significant interactions between any of the significant predictors of outcome retained in the final model.

The relative contribution of significant individual predictors to the explained variance of poor outcome in the final multiple logistic regression model is shown in Figure 2. Fever, anemia, and hyperglycemia contributed equally to risk of death or moderate to severe disability, whereas hyperglycemia showed a stronger relative association with mortality alone. The relative contributions of aneurysm size >10 mm and infarction from vasospasm to risk of poor outcome were insignificant in this analysis.

During the first 10 days after SAH, the mean difference in daily peak body temperature between febrile and nonfebrile patients was 1.4°C ($p = .004$), the mean difference in daily peak glucose level between hyperglycemic and nonhyperglycemic patients was 1.7 mmol/L ($p < .001$), and the mean difference in minimum hemoglobin level was 2.1 mg/dL ($p < .001$). These complications were mildly intercorrelated with each other (Pearson coefficient of 0.34 for fever and anemia, 0.27 for fever and hyperglycemia, and 0.21 for hyperglycemia and anemia; all $p < .001$), indicating that the presence of one made the development of the others more likely.

DISCUSSION

Seventy-nine percent of our SAH population developed at least one medical complication. In the placebo group of the Multicenter Cooperative Aneurysm Study, all of the 455 patients recruited between 1987 and 1989 had one or more medical complications (18). The higher rate of complications in the Multicenter Cooperative Aneurysm Study may reflect more liberal adverse-event reporting practices specific to clinical trials, more stringent definitions for complications in our study, or both.

Fever is a frequent event in neurocritical care patients (26). Fifty-four percent of our patients with SAH were febrile during their hospital stay. The lower fever rate of 29% in the Cooperative Aneurysm Study could be a result of exclusion of poor-grade patients or those with severe complicating medical problems (18). In another single-center study, fever occurred in 41% of 92 patients with SAH and was found to be associated with an increased risk of symptomatic vasospasm and poor outcome (27), a finding that we have also confirmed (28). Fever exacerbates ischemic injury (29), worsens cerebral edema and increased ICP (30), and may lead to decreased level of consciousness (28). Fever is also a common component of the systemic inflammatory response syndrome, which has been shown to predict poor outcome for patients with SAH (31). The use of fever-control interventions involving core temperature–controlled surface or endovascular cooling devices after SAH deserves further study.

Thirty-six percent of our patients with SAH were affected by anemia treated with transfusion, a frequency similar to that reported from the Cooperative Aneurysm

Table 3. Significant predictors of poor outcome at 3 months (modified Rankin Scale score of 4–6)

Feature	No. (%) Affected (n = 576)	Adjusted Odds Ratio (95% Confidence Interval) for Poor Outcome	*p* Value
Age, yrs	53 (16–89)	1.1 (1.0–1.1)	<.0001
Aneurysm size >10 mm	116 (23)	2.3 (1.3–4.0)	.003
Hunt and Hess grade	I: 160 (28) II: 80 (14) III: 178 (31) IV: 84 (15) V: 74 (13)	1.9 (1.5–2.4)	<.0001
Aneurysm rebleeding	58 (10)	7.2 (3.0–17.4)	<.0001
Infarct due to vasospasm	77 (14)	1.9 (1.0–3.6)	.06
Fever	309 (54)	2.0 (1.1–3.4)	.02
Anemia	206 (36)	1.8 (1.1–2.9)	.02
Hyperglycemia	174 (30)	1.8 (1.1–3.0)	.02

Data are shown as number (%) for dichotomized variables or median (range) for abnormally distributed continuous variables. Binary logistic regression was used to calculate *p* values and adjusted odds ratios (with 95% confidence intervals) for poor outcome, defined as death or moderate to severe disability (modified Rankin Scale score of 4 to 6) at 3 months.

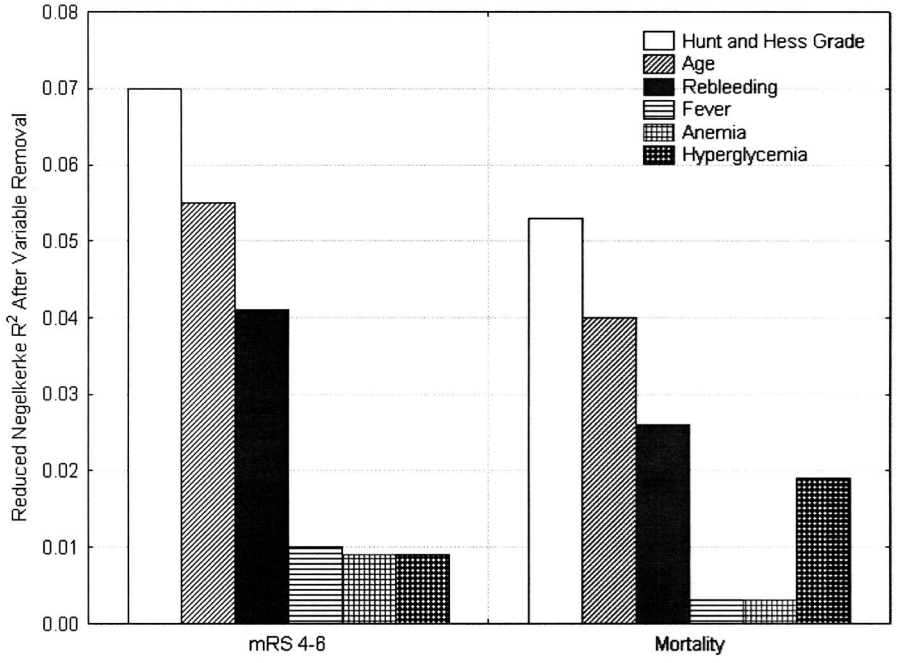

Figure 2. Relative contribution of significant individual predictors to the explained variance (Nagelkerke R^2) of poor outcome (death or moderate to severe disability) or mortality (modified Rankin Scale [*mRS*] score, 4–6) in the final multivariate logistic regression model.

Study (37%) (18). Interestingly, the occurrence of gastrointestinal hemorrhages in our population was only 4%. Consequently, anemia in our patients most likely resulted from the combined effects of an SAH-related reduction in red blood cell mass (32), bed rest, phlebotomy, and hemodilution from fluid administration. It is possible that anemia may directly contribute to poor outcome because of detrimental effects on cerebral oxygen delivery or its treatment with blood transfusions. A retrospective analysis of 441 patients with SAH showed that 61% received a blood transfusion during their hospital stay, which was associated with symptomatic vasospasm and worse outcome (33). In another study, blood transfusions were significantly associated with worse outcome for patients with SAH with vasospasm (34). Efforts directed at prevention of anemia after SAH with erythropoietin deserve further study (35), particularly given its potential neuroprotective properties (36).

Hyperglycemia exceeding 11.1 mmol/L (200 mg/dL) at any point during hospitalization occurred in 30% of our study cohort. Elevated glucose levels are known to have an adverse effect on outcome for patients with acute ischemic stroke and to increase the likelihood of intracranial hemorrhage after thrombolytic therapy (37–40). Strict glucose control has also been linked to reductions in intracranial pressure, duration of mechanical ventilation, and seizures in critically ill neurologic patients (41), and it has been shown to reduce mortality among critically ill surgical ICU patients (42). Although we found hyperglycemia to have an adverse effect on SAH outcome, prior studies of admission glucose levels after SAH have yielded inconsistent findings: one study showed a significant independent association with poor outcome (43), but another failed to confirm this relationship (44). Studies analyzing the impact of hyperglycemic burden over time on long-term SAH outcome are needed, as are trials of intensive insulin therapy for this disease.

Hyponatremia (<130 mmol/L) has been noted in approximately 30% to 40% and hypernatremia (>145 mmol/L) in approximately 20% of patients with SAH (45, 46). In our cohort, hyponatremia occurred in only 14%, which might be explained by the standardized administration of isotonic saline solutions and strict avoidance of free water (47). However, hyponatremia did not have any prognostic significance in our study, nor has it in others (46). The 22% frequency of hypernatremia (>150 mmol/L) in our study almost certainly reflects treatment for cerebral edema with mannitol or hypertonic saline solutions and therefore was mostly iatrogenic; only 4% of our patients had diabetes insipidus. Hypernatremia was highly correlated with poor outcome in the univariate analysis, but it was excluded from the multivariate analysis because it most likely reflects the adverse impact of a neurologic complication (brain edema and intracranial hypertension) rather than a medical complication *per se*. In another analysis of 298 patients with SAH, hypernatremia was independently associated with poor outcome, but the treatment of these patients was not described (48).

Pulmonary complications in our study, including pneumonia (20%), pulmonary edema (14%), pneumothorax

We identified three common medical complications—fever, hyperglycemia, and anemia—that significantly predict poor outcome after subarachnoid hemorrhage.

(3%), and pulmonary emboli (0.3%), occurred with nearly the same frequency in the Cooperative Aneurysm Study (18). Pulmonary problems were responsible for 50% of all fatal medical complications in the Cooperative Aneurysm Study (18). Pneumonia has also been associated with a three-fold increased risk of death at 30 days for acute stroke patients (49), and pulmonary complications have been linked to an increased frequency of symptomatic vasospasm after SAH, which may be due to less aggressive hypertensive and hypervolemic therapy (50).

Our study has several limitations. The generalizability of our findings is limited by the single-center design. Many medical complications of SAH may be iatrogenic, and hence their frequency and severity may have been influenced by our management protocol. Despite clear definitions, interobserver bias may have affected the accuracy of categorizing various complications. Finally, a larger study cohort may have increased our ability to identify additional complications that contribute to poor outcome.

CONCLUSION

We identified three common medical complications—fever, hyperglycemia, and anemia—that significantly predict poor outcome after SAH. However, it remains to be seen whether intervention targeted at preventing or treating these complications can improve outcome. Until more data are available, our findings support the practice of maintaining normothermia with systemic cooling devices and normoglycemia with continuous insulin infusion, as well as the administration of erythropoietin to prevent severe anemia and blood transfusions.

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