Outcome in patients with a poor prognosis after subarachnoid hemmorrhage

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OUTCOME IN PATIENTS WITH A POOR PROGNOSIS AFTER SUBARACHNOID HEMORRHAGE

Seagull

Cry into the wind
your helplessness
persist within a force too
big
your poignancy
your mastery
your commitment to the
deep.

Learn your true strength
in heart's hidden storm-
the needle point
that pulls the thread
against the odds of being.

Ride, ride again
elemental waves-
see fingers of flung might
that feel the storm
fashioning your pathos.

Cry into the wind
your empathy
your only fear be loss of this
for you belong
inside the storm-
the hope inside the crying.

Myra Vennard
Easter saturday, 2009

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JANTIEN HOOGMOED

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Outcome in patients with a poor prognosis after subarachnoid hemorrhage

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Faculteit der Geneeskunde

Contents

CHAPTER 1:

General introduction and outline

GENERAL INTRODUCTION AND OUTLINE

Epidemiology

A subarachnoid hemorrhage (SAH) from a ruptured intracranial aneurysm accounts for around 1-10% of all strokes[1,2]. It occurs at a relatively young age, with a mean age around 55 years[1]. It has an incidence of around 0.03 to 0.2 per 1000 person years[3]. The incidence in women is 1.2 times higher than for the male population[1,3]. This higher incidence starts at the age of 55 and increases with older age[1]. In spite of advancements in medical technology and treatment, the general incidence has decreased little in the past four decades[1,4].

Aneurysms

In approximately 85% an SAH is caused by an intracranial aneurysm. Ten percent of the SAH's are caused by non-aneurysmal perimesencephalic hemorrhages. The other 5% arise from rare causes; such as arteriovenous malformations, arterial dissections, various forms of intracranial arteritis, tumors and trauma, or remain a non-aneurysmal SAH (but blood distribution on the CT-scan is too widespread to meet the criteria of perimesencephalic)[2,5]. Around 3% of the population has an intracranial aneurysm[6,7]. The incidence of aneurysms increases with age, especially in women[6]. However, most intracranial aneurysms are, and remain, asymptomatic.

Intracranial aneurysms arise from sites of arterial branching, usually from the circle of Willis or branching nearby the circle. They form as a result of hemodynamic, genetic, hormonal, environmental and inflammatory factors. Smoking and hypertension increase the risk of aneurysm formation significantly[8,9].

The one and five year risk of rupture of an aneurysm is approx. 1.4% and 3.4%, respectively[10]. The risk of rupture increases, amongst others, with an advancing age, and varies depending on aneurysm size and location, ethnicity and previous hemorrhage. These variables have been used to create a prediction tool (PHASES) for risk of rupture[10]. The risk factors for the development of an SAH are displayed in table 1.

Table 1. Risk factors for an SAH

	RR (95% CI)	OR (95% CI)
Smoking	1.9 (1.5-2.3) – 7.3 (3.8-14.3)[8]	3.1 (2.7-3.5) – 3.5 (2.9-4.3)[8]
Hypertension	1.6 (1.2-2.0) – 3.4 (2.3-5.7)[8,10]	2.3 (1.7-3.2) – 2.9 (2.4-3.7)[8]
Excessive alcohol consumption	2.1 (1.5-2.8) – 4.7 (2.1-10.5)[8]	1.5 (1.3-1.8)[8]
Female sex	1.2 (0.9-1.7)[10] – 2.1 (1.1-3.9)[11]	n/a
Posterior circulation	2.5 (1.6-3.7)[10] – 4.1 (1.5-11.0)[11]	n/a
Diabetes Mellitus	0.3 (0-2.2)[8]	0.7 (0.5-0.8)[8]
Hypercholesterolemia	n/a	0.4 (0.2-0.7) – 0.6 (0.4-0.9)[8]
Hormone replacement therapy	n/a	0.5 (0.3-0.9) – 0.6 (0.4-0.9)[8]
Ethnicity	North America and Europe (excluding Finland): Reference Japan: 2.0 (1.4-2.9) Finland: 2.4 (1.5-4.1)[10]	n/a
Cocaine[*]	n/a	12.2 (1.4-103.7)

[*]Usage in the week preceding the SAH
SAH Subarachnoid hemorrhage

Presentation after rupture

Around 12% of the patients presenting with an SAH will die before, or during, transportation to a hospital[12]. Of the patients who reach the emergency room, around 30-40% are reported to have had a loss of consciousness (LOC) after the ictus[13,14]. In 60% of these patients the LOC will be temporary, but in 40% it will last longer than an hour. More than half (55%) of all patients with LOC will be classified as being comatose at presentation[13]. LOC in itself is associated with a poor clinical condition and a predictor of poor outcome in SAH patients[13,14].

In most (70%) patients the presenting symptom will be severe acute onset headache, described as the worst headache ever[2,5,15]. In a third of the cases this headache is accompanied with (transient) focal neurological deficits and will precede loss of consciousness[16]. Only a small subset of patients, 6%, presents with a seizure at onset[17]. Nuchal rigidity is a commonly found symptom in SAH patients as a response of blood in the subarachnoid space. This develops in 3-12 hours after the ictus and can be absent in deeply unconscious patients[18]. Some patients will be in a confusional state at presentation, which can make diagnosis difficult [19,20].

Grading patients

As LOC and the overall clinical state are associated with clinical outcome, different grading systems have been developed to try and predict prognosis. Traditionally, the Hunt and Hess (H&H) score[21] was widely used to assess the surgical risk of SAH patients (box 1). However, the H&H grade was found to have a high interobserver variability, feeding the need for an easier assessment tool. Because the clinical outcome seemed to greatly depend on the level of consciousness, and not so much on focal neurological signs, the World Federation of Neurological Surgeons (WFNS) set up a committee in 1981 to develop a new score, based on the Glasgow Coma Scale (GCS), used (worldwide) to assess the level of consciousness after neurotrauma (box 1). [22,23]. The aim of this new score was to have a standardized tool to estimate prognosis, to report research uniformly and to quantify a change in patient status over time. In recent years, newer grading scales, such as the Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage (PAASH) scale, have been proposed to better predict the outcome of patients[24]. The PAASH is easier to use and has as good interobserver variability as the WFNS scale and a more gradual risk increase for poor outcome in the higher categories compared to the WFNS (box 1). Despite these advantages, the WFNS, as well as the Hunt and Hess, are still the most commonly used grading scales[25]. Historically, they have been used the most, which makes comparison between series easier, but are probably not the best to predict clinical outcome.

Poor condition

About a third of the patients presents in a poor clinical condition, in literature most commonly defined as a H&H grade IV and V, or a WFNS grade IV and V[26,27]. A poor condition on admission is highly indicative for a poor long-term prognosis[13,28]. Only around a quarter of the poor-grade patients reaches a favorable outcome[29,30]. The causes of this poor condition vary widely; acute hydrocephalus and intraventricular hemorrhage may cause deterioration of a patient's initial neurological status[31]. A poor condition can also be caused by an intraparenchymal hemorrhage or a subdural hematoma, with a concomitant increase of intracranial pressure[32,33]. Early brain injury occurs in the acute state with an acute increase in intracranial pressure, decreased cerebral blood flow, disruption of the blood brain barrier, brain swelling and edema and global ischemia which compromises a patient's conscious level[13,34]. Seizures can be present at the debut of the hemorrhage, as stated earlier, and a postictal state may obscure the clinical assessment of a patient[35]. A recurrent bleeding from the causative aneurysm can also cause a deterioration to a poor clinical condition, right before or after admission[36].

Box 1

The **Hunt and Hess** score was developed in 1968. It was used by the authors preoperatively to determine which patients would benefit from aneurysm surgery. If a patient had an associated disease, which in the eye of the surgeon was severe enough to influence the operative and postoperative course, one point would be added to a patient's grade. Patients with a grade I and II were deemed most eligible for surgery. Grade III and higher would have to show clinical improvement before treatment would be initiated, with exception of patients with grade III and multiple rebleeds or a space occupying hematoma. Grade IV and V were treated with a very high threshold and only if they improved to a grade I or II[21].

Grade I	asymptomatic, or minimal headache or slight nuchal rigidity
Grade II	moderate to severe headache, nuchal rigidity, no neurological deficit other than cranial nerve palsy
Grade III	drowsiness, confusion, or mild focal deficit
Grade IV	stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances
Grade V	deep coma, decerebrate rigidity, moribund appearance

The **WFNS grade** is based on the Glasgow Coma Scale (GCS), comprised of three different responses: eye, motor and verbal[77]. A maximum score with full consciousness is 15, with a minimum score of 3 in deep coma.

WFNS grade	Glasgow Coma Scale	Motor disturbances
Grade I	15	absent
Grade II	13-14	absent
Grade III	13-14	present
Grade IV	7-12	absent/present
Grade V	3-6	absent/present

The **PAASH scale** is based on the GCS score and uses cut-off points between categories based on selection of the largest statistical difference in outcome at six months, in contrast to the WFNS, which was based on consensus[24].

PAASH scale	Glasgow Coma Scale
Grade I	15
Grade II	11-14
Grade III	8-10
Grade IV	4-7
Grade V	3

Besides these intracranial processes an SAH can also have extracranial complications which cause impairment of consciousness, such as cardiac dysfunction, including Tako-Tsubo cardiomyopathy, arrhythmias, and myocardial infarction[37–39]. These cardiac manifestations can sometimes lead to misdiagnosis of having a primary cardiac disease. Forty-three to 92% of the patients have oxygenation disturbances in the acute stage after an SAH, with a higher incidence in poor-grade patients[38,40]. Oxygenation disturbances can lead to neurogenic pulmonary edema (NPE), which occurs in 2-22% of all SAH patients[38]. NPE occurs mainly in patients with a poor clinical condition and is associated with a higher case fatality[38,40].

Rebleeding

After the initial hemorrhage patients are at danger of a recurrent bleed from the causative aneurysm; commonly called rebleeding in the literature. Around 16% of the patients experiences a rebleeding after an SAH and it causes significant mortality and morbidity[36,41–43]. The risk of rebleeding is the highest in the first hours after the ictus; 95% of the rebleeds occur in the first 24 hours, 80% even in the first 12 hours after the ictus[42,44]. Rebleeding can happen before the patient reaches the hospital; 40% of the rebleeds occur before a patient reaches a treatment center. Thirteen percent even happen at home or on the way to a primary hospital[42]. Risk factors for rebleeding are more intracranial blood (modified Fisher Score 3 and 4), an external ventricular catheter, a poor-grade SAH and a larger or irregularly shaped aneurysm[44–46]. In poor-grade patients the occurrence of a rebleed further diminishes their chances of a good outcome[36,44,47]. Seventy percent of the poor-grade (WFNS grade IV and V) patients who experience a rebleed will have died before discharge[36]. Therefore, prevention of rebleeding is of utmost importance.

Treatment

Occlusion of the aneurysm is directed not only at prevention of rebleeding in the short term but also in the long term. For many decades surgical clipping was the mainstay of aneurysm treatment. Nowadays, this is replaced by endovascular coiling in the majority of patients. Endovascular coiling reduces the risk of death and dependency compared to surgical clipping (absolute risk reduction 7% after one year) and is the preferred treatment for patients in a good clinical condition and for whom both treatment modalities are possible[48,49]. For patients in a poor clinical condition it seems that endovascular treatment is preferential as well, however, no prospective evidence is available at the moment[48,50,51]. Surgical clipping is however, still being performed in patients with complex aneurysms, not suitable

for endovascular procedures and in patients with concomitant space occupying hematoma that needs decompression.

In the past, aneurysm treatment, i.e. surgical clipping, was initiated after a couple of days[52,53]. In the seventies and eighties, surgery within 7 to 9 days was seen as 'early,' and it was thought that early surgery was associated with more cerebral ischemia due to vasospasm. The consensus was therefore, to wait at least 10 to 14 days for the period of vasospasm to subside[21,53–55]. In the last 20 years the shift has been more towards earlier treatment: within three days after admission[52,56,57]. This not only to prevent the risk of rebleeding, but also to avoid treatment during the period of vasospasm. But as the risk of rebleeding is the highest in the first hours after the ictus, it seems rational to perform aneurysm treatment as soon as possible after admission[58–60]. However, this subject is still debated and it remains a focus of future research[59,61].

Treatment of patients in a poor condition after the SAH is also still a major point of discussion. Traditionally, these patients were treated conservatively and treatment was only initiated if they showed signs of spontaneous neurological improvement[21,55,62]. This creates a delay in treatment in these already vulnerable patients, leaving them susceptible to further deterioration from rebleeding. This deterioration will not only worsen the outcome but will also raise the threshold to initiate treatment. In recent years there have been recommendations to proceed towards treatment in poor-grade patients and preferably as early as possible[28,61,63,64]. However, in everyday practice, many poor-grade patients are still being treated conservatively, because of the expectation that they will reach a poor outcome anyway. This is especially true for patients in the poorest condition; H&H V or WFNS grade V. The downside of aggressive and early treatment of these patients is the fact that treatment can be futile in patients in the poorest clinical condition. Even with optimal treatment, a significant portion of these patients will die in the course of the disease and would possibly be exposed to unnecessary treatment. But more importantly, with optimal treatment a portion of patients in a poor condition will survive and will not improve to a good clinical condition. Sadly, these patients remain dependent on daily care.

Secondary complications

After surviving the first hours after an SAH, a patient is still at risk of further complications. These secondary complications can occur either in the acute phase or later during the admission period.

Hydrocephalus occurs in 15%-87% of the patients within 72 hours after admission, depending on the definition of hydrocephalus[2,31,50]. It has a relation with intraventricular blood and most patients experience a decrease of consciousness[5,31]. However, one in five patients with enlarged ventricles on a CT-scan will be alert. When patients are drowsy, but stable, a watchful waiting policy can be safe as about half of the patients improve within 24 hours[65]. If treatment is necessary, acute hydrocephalus is treated, depending on the characteristics, by external ventricular drainage (EVD), external lumbar drainage (ELD) or repeat lumbar puncture. Persistent hydrocephalus, requiring permanent shunting, is present in 7%-48% of the patients[5,50,66]. An increased age, poor grade, intraventricular hemorrhage, meningitis, and delayed cerebral ischemia are associated with a higher incidence of shunt dependency[66].

Delayed cerebral ischemia (DCI) typically occurs between the 4th and 14th day after the hemorrhage[67]. It occurs in about 30% of the patients and is a major contributor to morbidity and mortality after an SAH, depending on the definition used[41,67,68]. Nowadays, DCI is defined according to the criteria by Vergouwen et al.: "The occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least two points on the Glasgow Coma Scale (either on the total score or on one of its individual components [eye, motor on either side, verbal]). This should last for at least one hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies"[67]. In the past, new ischemic events and/or new neurological deficits after an SAH were thought to have been caused by narrowing of the cerebral arteries (i.e. vasospasms). However, patients sometimes remain completely asymptomatic with extensive vasospasm (visible on angiogram) and patients sometimes have widespread ischemia with very mild vasospasms[50,67]. As the pathogenesis of DCI is still not well understood and the diagnosis is notoriously difficult to make, definite treatment is not available to date. Nimodipine was initially used to prevent vasospasms, but it does not have an effect on large-vessel vasospasms. It has been shown to reduce the risk of poor outcome and secondary ischemia[50,68]. Other preventive actions are euvolemia and prevention of hyponatremia. When DCI occurs some advocate the use of endovascular angioplasty, whilst others advocate induced hypertension, however, none of these have been proven beneficial for clinical outcome[5,50,68].

As for all patients admitted to hospital, patients with an SAH are at risk of developing hospital-acquired infections, also known as nosocomial infections. Almost 40% of the SAH patients experience a nosocomial infection[69]. The occurrence of nosocomial infections are associated with the severity of the SAH, with a higher incidence in the poorest-grade patients[69]. The most frequently reported nosocomial infections are urinary tract infections (9%-24%) and pneumonia (17%-23%)[69,70]. These occur mostly in the first week after the hemorrhage[69]. Another important infection which can occur after SAH is a meningitis or ventriculitis. In SAH, up to 4% of the patients are diagnosed with a CNS infection[69,70]. Bacterial meningitis/ventriculitis develops readily in patients with an external ventricular or lumbar catheter or after a craniotomy and mostly occurs after the first week following the ictus[69]. A 'sterile', aseptic or inflammatory, meningitis/ventriculitis after SAH, caused by the presence of blood products in the cerebral spinal fluid, can be difficult to distinguish as the symptoms (fever, nuchal rigidity, decreased level of consciousness) are the same as in bacterial meningitis.

Nosocomial infections are in general associated with a longer ICU and hospital stay, and especially so in SAH patients. Patients with nosocomial infections after SAH have a decreased quality of life and a poorer outcome, including a higher mortality rate[70,71].

Clinical outcome

Subarachnoid hemorrhage, overall, is a devastating disease with a mortality rate of around 50%, with 12% of the patients dying before reaching the hospital[12,65]. As people are affected in their productive life years, the burden on society is as much as the more prevalent ischemic stroke, which mostly affects elderly[72,73]. The case-fatality of an SAH ranges between 8% and 67%, depending on the region of the world where a patient lives, with the lowest case-fatality in Japan.[3,4,74]. Over the last decades, the case-fatality rate of an SAH has dropped with 0.6% per year[74]. This indicates that treatment and care have greatly improved, however, it still remains a devastating disease.

Between 36% and 56% of the SAH patients will regain independence in daily living (modified Rankin Scale score 0-3) between one and 12 months after the hemorrhage[27,73]. Even though these patients are independent, it does not mean they do not face difficulties in daily life. Cognitive impairment is a major cause of disability and memory deficits occur in a little over half of the patients[73]. Up to

75% of the patients experience impairments in executive functions and language, and about half have problems with anxiety and depression[73,75]. Due to these disturbances only around a third of the good-outcome patients are able to return to a job at their previous level. These disabilities and loss of productiveness in society cause a reduced quality of life for these patients and their family[73].

A quarter of the surviving SAH patients reaches a poor outcome and depends on daily care and will be mostly discharged to nursing homes[27,62]. This however, does not mean that they stay there; one in three will return to live at home within two years[73]. A strong predictor for a poor outcome is a poor clinical condition on admission[30,76]. The rate of a good outcome (modified Rankin Scale score 0-2) for poor-grade patients has improved between the seventies and nineties, from 13% to 35%. However, it has remained unchanged in the recent years, with still the majority of the poor-grade patients reaching a poor outcome, including death[30]. It remains a challenge to improve the outcome in patients who have a poor prognosis, either because of their clinical condition at admission or because of other factors, such as rebleeding or infections, which compromise their clinical status.

Aims and outline of this thesis

This thesis focuses on outcome in SAH patients who are considered to have a poor prognosis. In part 1 factors contributing to a poor outcome are explored, including rebleeding and meningitis, and in part 2 we discuss the characteristics and treatment approach of patients who are already in a poor clinical condition at admission in order to try to select those patients who will benefit most from aggressive treatment.

After a short introduction of several aspects of aneurysmal SAH (**Chapter 1**), we focus on early treatment to prevent rebleeding. As rebleeds are a major contributor to poor outcome in patients after an SAH, we explore the time intervals between the moment of the SAH and the initiation of aneurysm treatment and the factors contributing to delay (**Chapter 2**).

Although nosocomial bacterial meningitis is extensively studied in the presence of an external ventricular catheter in neurosurgical patients in general, this has not been done in solely SAH patients. Infections after an SAH are known to be associated with poor outcome. The presence of blood in the cerebrospinal fluid

(CSF) hampers the diagnosis of a bacterial meningitis. In **Chapter 3** the prevalence of bacterial meningitis in SAH patients and the diagnostic challenges in this specific patient group is studied.

A better understanding of the cause of death of poor-grade patients may give rise to opportunities to prevent death in some cases. In **Chapter 4** we explore the reasons of demise in poor-grade SAH patients. Maybe a more expeditious treatment of poor-grade patients could lead to a better outcome.

The general approach to poor-grade SAH patients in a majority of centers worldwide is to institute a conservative treatment until spontaneous neurological improvement occurs. Only then is treatment of the aneurysm considered. In **Chapter 5** a more expeditious treatment approach is compared to the more usual conservative treatment approach to determine whether aggressive treatment of the poorest-grade SAH patients leads to a better clinical outcome and more surviving patients.

The question remains how to select those patients who will benefit from this aggressive treatment, as medical resources are not infinite. Also, not to expose patients to unnecessary treatment if treatment in their case would be futile. **Chapter 6** describes the disease-related characteristics present at admission. These characteristics are investigated to better identify those patients who will benefit from expeditious treatment.

Chapter 7 discusses the main findings of this thesis and possible directions of future research are proposed. **Chapters 8 and 9** contain a summary in English and Dutch, respectively.

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CHAPTER 2:

Time intervals from aneurysmal subarachnoid hemorrhage to treatment and factors contributing to delay

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ABSTRACT

Introduction: In the management of aneurysmal subarachnoid hemorrhage (aSAH), aneurysm treatment as early as feasible is mandatory to minimize the risk of a rebleed and may thus improve outcome. We assessed the different time intervals from the first symptoms of aSAH to start of aneurysm treatment in an effort to identify which factors contribute mostly to a delay in time to treatment.

Methods: In 278 aSAH patients, time intervals between the different steps from initial hemorrhage to aneurysm treatment were retrospectively reviewed, and delaying factors were determined.

Results: Half of the patients presented to a hospital within 115 minutes (IQR 60-431). The median (IQR) interval from hemorrhage to diagnosis was 169 minutes (96-513), and from diagnosis to treatment 1057 minutes (416-1428), or 17.6 hours. Aneurysm treatment started within 24 hours in 76% of treated patients. Independent factors predicting delay to treatment were primary presentation at a referring hospital and admission to the treatment center later in the day. Delay in treatment was not independently related to poor outcome.

Conclusions: The interval to aneurysm treatment might be improved upon by immediate and direct transport to the treatment center combined with optimization of in-hospital logistics, following the 'time-is-brain' concept so successfully adopted in the treatment of ischemic stroke.

INTRODUCTION

An aneurysmal subarachnoid hemorrhage (aSAH) is a medical emergency with an in-hospital case fatality rate of 35%[1]. The outcome of patients who have experienced an aSAH is very likely affected by the timing of diagnosis and treatment. The optimal timing of treatment has been a point for discussion for several years[2–7]. Nowadays, there is consensus on the value of securing the aneurysm as early as feasible[8,9] as the most threatening complication in the initial phase after an aSAH is a rebleed[2,10], which is an independent predictor for poor outcome[3,4,8]. Recently, it was reported that patients are more likely to die when treated in lowest volume hospitals[11], but transfer of the patient after diagnosis, and longer duration of the transfer, might be associated with an increase in unfavorable outcome[11–13].

Many factors hinder the expedition of care, as shown by a recent study in Greater London where treatment was significantly delayed in 75% of good grade SAH patients[14], and also by a delay in treatment in patients with a longer time to first presentation and diagnosis[15]. As delaying factors thwart efforts to effectively secure aneurysms ultra-early, i.e. within 24 hours after initial hemorrhage and even earlier if feasible, more insight is necessary in the specific time intervals and the factors related to delay in these intervals, in order to optimize ultra-early treatment. The aim of this study was to assess as accurately as possible the different time intervals from the first symptoms of aSAH to start of aneurysm treatment, and to determine which factors delayed treatment. Additionally, we investigated whether the time intervals or the delaying factors were related to outcome.

METHODS

Patient population

From November 2008 to July 2011, 300 patients with an aSAH were admitted to our hospital, a referral center for the treatment of SAH patients in a region of approximately 1.3 million people. Twenty-two patients were excluded: five because they presented more than one week after the hemorrhage, one because it took more than one week to diagnose the SAH and another because of posterior reversible encephalopathy syndrome. Fifteen patients, diagnosed by lumbar puncture (LP) at least 12 hours after the onset of headache, were excluded because the inherent delay in diagnosis interfered with our policy of ultra-early treatment. The diagnosis of the included patients was established by computed tomography (CT), and the aneurysm

that was held responsible for the hemorrhage was demonstrated by CT-angiography (CTA) and/or digital subtraction angiography (DSA). All DSA investigations and the majority of CTAs were performed at our center.

Data collection

All medical records, radiological investigations, ambulance data and referral letters were reviewed retrospectively with approval of the Medical Ethics Committee of the Academic Medical Center, Amsterdam. Lacking data from referring hospitals were retrieved. We recorded patient demographics, referring hospital, World Federation of Neurological Surgeons (WFNS) grade[16] at primary presentation to a medical facility, dates and times (of hemorrhage, primary presentation, diagnosis and treatment) and treatment modalities (clipping, coiling or none). If a patient was not admitted primarily to our center but was referred from another hospital, the date and time of presentation at our center was recorded as well.

Clinical outcome was scored using the modified Rankin Scale (mRS)[17] by reviewing the medical records of the outpatient clinic at follow-up or the letter from the rehabilitation center. If no exact initial hemorrhage time, i.e. time of onset of SAH, was known, it was approximated based on information about the patient's activity during which the SAH occurred, such as "going to work" or "during dinner", if mentioned in the medical records. To approximate the hemorrhage time as reliable as possible, we developed a checklist containing standard activities throughout the day linked to a specific time point. Three authors (MG, HvS and DV) approximated the hemorrhage time independently based on the information in the medical records and the checklist, with the assumption that the hemorrhage occurred at least one hour before admission. In case of inconsistencies, consensus was achieved after discussion. In case of finding a patient unconscious, the time point in between last seen healthy and time of discovery was reported as the hemorrhage time. If no time could be retrieved it was recorded as 'irretrievable'.

Clinical management

All patients were treated according to our standardized protocol which closely follows international guidelines[8,9]. In short, on admission to the intensive care unit or medium care facility, an adequate blood pressure to optimize cerebral perfusion is maintained but severe hypertension is avoided. An adequate oxygenation, pH value and diuresis are maintained at a standard intake of at least 2L fluids/day. Standard medications are nimodipin, low molecular weight heparin prophylaxis,

acetaminophen analgesia, supported with additional analgesics when necessary, and laxatives. When patients are admitted with a WFNS grade 4 or 5 and enlarged ventricles on the CT they receive cerebrospinal fluid (CSF) diverting treatment, which usually contains external ventricular catheter placement. Patients with a WFNS grade 1-3 only receive CSF-diverting treatment on indication. All aneurysms are secured as early as feasible, preferably within 24 hours after the last hemorrhage, and within daytime hours (8 a.m.-10 p.m.), unless dictated otherwise by the patient's clinical condition. The choice of treatment modality (clipping, coiling or none) is made in consensus between neurologist, neurosurgeon and interventional neuroradiologist.

Statistical analysis

Time points during the day were outlined on a 24-hour scale, starting at 12 o'clock midnight (00:00). Consequently, a time point later in the day relates to a longer interval from midnight. Time intervals were computed by calculating the difference between the retrieved time points. The WFNS grades and mRS scores were dichotomized into groups with a good (WFNS grade 1-3) or poor grade (WFNS grade 4-5), and into groups with a favorable (mRS 0-3) or poor outcome (mRS 4-6), respectively. Normally distributed variables were expressed as means with standard deviations (SD) and tested with the Student's t-test (two group comparison); unequally distributed variables were expressed as medians with interquartile ranges (IQR 25%-75%) and tested with the Mann-Whitney U test (two group comparison) or Kruskal-Wallis test (multiple group comparison). The Chi-square test was used to assess differences in proportions. Spearman's rho was used to assess the relation between two continuous variables (with at least one unequally distributed variable).

Univariate analyses were performed to assess the predictive value of potential predictors on both delays in the different time intervals and poor outcome. The potential predictors were based on previous literature and included age (in years), WFNS grade, type of treatment, time of initial hemorrhage, diagnosis and admission to treatment center (all on 24 hours-scale), and presentation at referring hospital or treatment center[12,13,18,19]. With respect to outcome, the different time intervals were also included in the univariate analysis as potential predictors. To identify parameters that are independently related to delay between diagnosis and treatment, a multivariate backward linear regression analysis was performed including the parameters that were significantly related to delay in the univariate

analysis. The time interval between diagnosis and treatment was log transformed to obtain a normal distribution. Values of the standardized betas were transformed back to normal values. To identify parameters that are independently related to poor outcome, a multivariate backward logistic regression analysis was performed including the parameters that were significantly related to poor outcome in the univariate analysis. A p-value <0.05 was considered significant. All analyses were performed using SPSS Statistics.

RESULTS

Patient characteristics

The mean (SD) age of the 278 patients was 56.2 years (12.5) and 64% was female (table 1). About one-fifth of all patients presented primarily at our center. Twenty hospitals referred their patients to our center, ranging from 1 to 46 patients per hospital with twelve hospitals referring at least five patients. The median (IQR) distance between the referring hospitals and our center was 18.6 miles (11.6-33.9). Patients presenting at a referring hospital significantly more often had a good WFNS grade and endovascular treatment when compared to patients presenting at the treatment center (table 1).

Table 1. Baseline characteristics of 278 patients with aneurysmal subarachnoid hemorrhage

		Hospital of primary presentation		
Patient characteristics	**Total** (n= 278)	**Treatment center** (n= 59)	**Referring hospital** (n=219)	**p-value**
Age, years	56.2 ± 12.5	55.3 ± 11.6	56.4 ± 12.7	0.55[a]
Female	179 (64)	37 (63)	142 (65)	0.76[b]
WFNS at presentation				<0.01[b]
1-3	172 (62)	26 (44)	146 (67)	
4-5	106 (38)	33 (56)	73 (33)	
Treatment modality				
clip	30 (11)	11 (19)	19 (9)	
coil	215 (77)	39 (66)	176 (80)	
none	33 (12)	9 (15)	24 (11)	0.04[b]

Data are shown as n (%) or mean ± standard deviation (SD), *WFNS* World Federation of Neurological Surgeons

[a] Student's t-test, [b] Chi-square test

Time data

Not all time points could be retrieved and therefore not all patients were used to calculate the time intervals (table 2). The exact time of initial hemorrhage could be retrieved in 127 patients (46%), was approximated in 133 patients (48%), and was irretrievable in 18 patients. There were no significant differences between the three groups in distribution of dichotomized WFNS grade (P=0.91).

Time intervals

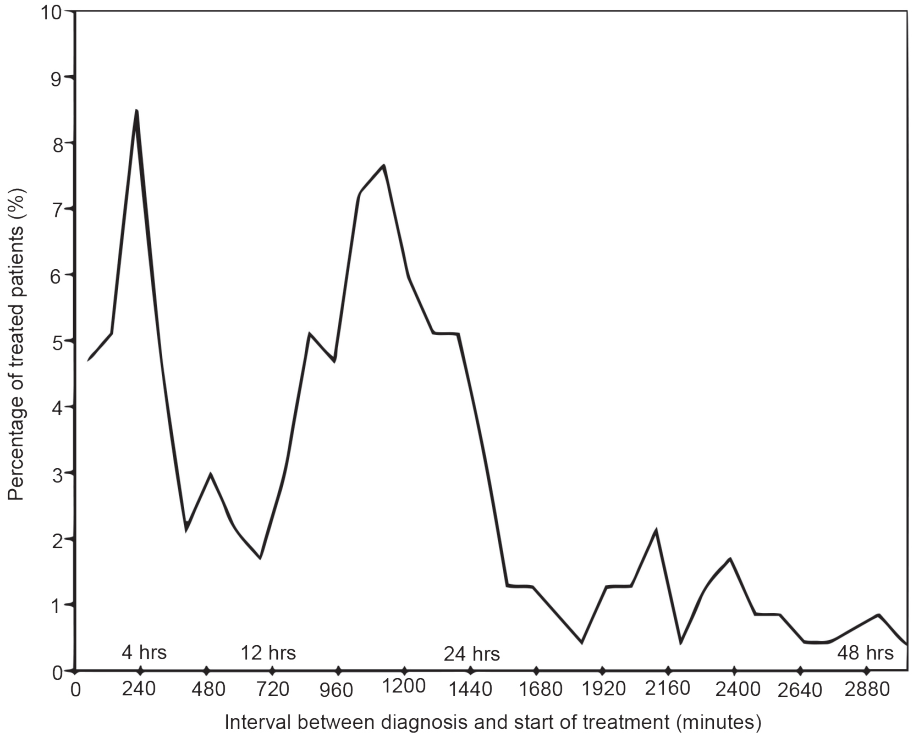
The median (IQR) interval from initial hemorrhage to diagnosis was 169 minutes (96-513) (table 2). When patients presented at a referring hospital, the median time interval (IQR) between diagnosis at the referring hospital and admission to the treatment center was 114 minutes (89-155). Half of the patients was treated within 1057 minutes (IQR 416-1428) (17.6 hours) after diagnosis. Aneurysm treatment started within 24 hours after diagnosis in 179 patients (76% of treated patients with established time interval). Percentages of patients treated at different time intervals show peaks in frequency of treatment at approximately 240 and 1140 minutes (4 and 19 hours, respectively) after diagnosis (figure 1).

Table 2. Different time intervals in 278 patients with aneurysmal subarachnoid hemorrhage

Type of time interval	Number of patients (n=278)	Time intervals (minutes)	
Initial hemorrhage to presentation	244 (88)	115 (60-431)	**Before diagnosis**
Presentation to diagnosis	248 (89)	26 (11-58)	
Initial hemorrhage to diagnosis	252 (91)	169 (96-513)	
Diagnosis to admission treatment center	120 (55[a])	114 (89-155)	**After diagnosis**
Diagnosis to start of treatment	235 (96[b])	1057 (416-1428)	

Data are shown as n (%) or medians (interquartile range), [a] of referred patients, [b] of treated patients

Figure 1. Frequency distribution (in %) of 247 patients treated at different time intervals from diagnosis to start of treatment



Factors predicting delay

A delay in all separate time intervals was significantly related to a good WFNS grade and primary presentation at a referring hospital (table 3). A longer time interval between initial hemorrhage and both presentation and diagnosis was significantly related to older age and later admission to the treatment center. Furthermore, a longer time interval between diagnosis and treatment was significantly related to later admission to the treatment center. There were no other significant relations between longer time intervals and potential predictors in the univariate analysis.

The multivariate analysis showed that presentation at a referring hospital (standardized Beta (95% CI): 1.4 (1.2-1.6)) and admission to the treatment center later in the day (standardized Beta (95% CI): 1.3 (1.1-1.5)) were independently related to a longer time interval between diagnosis and treatment (adjusted R^2: 14%, ANOVA total multivariate model $P<0.01$). The delaying influence of primary presentation at a referring hospital on the different time intervals is illustrated in

table 4. Significantly more patients were treated within 24 hours when the primary presentation was at the treatment center, compared to primary presentation at a referring hospital (89% and 73%, respectively; *P*=0.02).

Table 3. Univariate analysis of the relation between different time intervals and significant predictors for delay

	Type of time interval				
Potential predictors	**Initial hemorrhage to presentation**	**Presentation to diagnosis**	**Initial hemorrhage to diagnosis**	**Diagnosis to admission treatment center**	**Diagnosis to start of treatment**
Age[a]	0.04	n.s.	0.03	n.s.	n.s.
WFNS at first presentation (1-3 vs 4-5)[b]	<0.01	<0.01	<0.01	0.02	<0.01
Time point of admission in treatment center[a]	<0.01	n.s.	<0.01	n.s.	<0.01
Primary presentation at treatment center vs. referring hospital[b]	0.02	<0.01	<0.01	n/a	<0.01
	Before diagnosis			**After diagnosis**	

n.s. not significant; *WFNS* World Federation of Neurological Surgeons; n/a not applicable
[a] Spearman's rho
[b] Mann-Whitney U test

Table 4. Time intervals in patient groups according to hospital of primary presentation

	Hospital of primary presentation			
Type of interval	**Treatment center**	**Referring hospital**	**p-value**[a]	
Initial hemorrhage to presentation	92 (56-213)	130 (64-522)	0.02	**Before diagnosis**
Presentation to diagnosis	14 (4-40)	30 (14-63)	<0.01	
Initial hemorrhage to diagnosis	114 (62-261)	175 (105-599)	<0.01	
Diagnosis to admission treatment center	-	114 (89-155)	n/a	**After diagnosis**
Diagnosis to start of treatment	388 (116-1093)	1123 (709-1488)	<0.01	

Data are shown as medians (interquartile range)
n/a not applicable
[a] Mann-Whitney U test

Outcome

Outcome assessment was performed in 264 patients at a median (IQR) interval of four months (2-7) after the hemorrhage. Of those patients, 35% had a poor outcome and 24% died. Higher age, poor WFNS grade, a shorter time interval between presentation and diagnosis, and no aneurysm treatment were significantly related to poor outcome. The multivariate analysis (OR (95% CI)) showed that higher age: 1.1 (1.0-1.1), poor WFNS grade at presentation: 4.1 (2.1-7.9), and no treatment (no treatment vs. coiling: 47.2 (6.0-368.2), no treatment vs. clipping: 47.9 (5.2-445.5)) were independently related to poor outcome (Nagelkerke R square: 40%, Hosmer & Lemeshow-test, p=0.366, Omnibus test total multivariate model $P<0.01$).

DISCUSSION

We assessed different time intervals from initial aSAH to start of aneurysm treatment and found relatively short intervals from initial hemorrhage to diagnosis and from diagnosis to treatment. However, our data also show that delays in aneurysm treatment seem to be caused by presentation to a referring hospital and by admission later in the day.

The median interval between diagnosis and start of treatment in our study was 18 hours, and in 76% of treated patients, treatment started within 24 hours. This is considerably faster than reported elsewhere[14,15]. An explanation for delay in aneurysm treatment is usually the impossibility to treat aneurysms 24/7 due to low admission numbers and a lack of routine provision of clipping at weekends and next day coiling services[15]. The policy in the referring hospitals is to transfer every SAH patient to our hospital, so 2-3 aSAH patients are admitted to our center each week. With four neurovascular surgeons and four interventional neuroradiologists we have the ability to treat the aneurysms 24/7 and strive to initiate aneurysm treatment as early as feasible, preferably during working hours. By performing the majority of CTA investigations and all DSA investigations in our center we have all necessary radiological investigation immediately available.

Multivariate regression analysis showed that primary presentation at a referring hospital, and admission to the treatment center later in the day were independent predictors for delay to treatment. The additional transfer to the treatment center after diagnosis at the referring hospital would be a reasonable explanation for the delay in these patients. However, the median time from diagnosis to admission

in the treatment center was only 114 minutes whereas the total delay in treatment was much longer (12 hours). Other reasons for this delay could be the addition of logistical steps, such as radiological investigations in the treatment center[20,21], or a lower sense of emergency treatment in these patients as their WFNS grade at the treatment center may have improved after first admission owing to clinical stabilization of the patient at the referring hospital. Unfortunately, since we only evaluated the WFNS grade at the primary presentation, we cannot confirm this with our data. Admission to the treatment center later in the day most likely introduces a delay due to the higher probability of postponement of treatment to the next day, especially because we do not perform aneurysm treatment between 10 p.m. and 8 a.m. unless there is a life-threatening situation or history of a rebleed. This could be reflected in our data which show peaks in the percentage of treated patients at 4 (same-day) and 19 hours (next-day) after diagnosis.

The overall outcome in our patient population is worse in comparison to large aSAH studies[18,22], but can be explained by our ultra-early treatment strategy which also includes all WFNS grade V patients[7,23,24]. Poor WFNS grade at admission, higher age, and absence of treatment were independently related to poor outcome. However, we found no significant relation between poor outcome and time interval between diagnosis and treatment. There are several explanations for the lack of finding this association. First, there are patients, both in the groups of good and poor WFNS grades, in whom improvement or deterioration in outcome is not possible, irrespective of their time to treatment. Second, since clinical practice is already aimed at aneurysm treatment as early as feasible, there is a substantial group of patients with a good outcome without a delay in treatment, which also may have distorted the association between time to treatment and outcome. Finally, clinical characteristics, such as delayed ischemic deficits, and surgical and medical complications are not taken into account in this study and may therefore make the outcome model incomplete. Therefore, although no significant association between ultra-early aneurysm treatment and good outcome was found in this study, we are convinced that this relation does exist[12,13] and evaluation of this relation needs to be performed either in large (multicenter) studies or in studies evaluating specific subgroups.

Our policy of ultra-early aneurysm treatment, i.e. all aneurysms are secured as early as feasible, shows similarities with thrombolysis in acute ischemic stroke. The ‘time-is-brain’ concept should perhaps be extrapolated to patients with an aSAH.

The proposed adjustments could include: 1) immediate and direct transportation to the treatment center if there is suspicion of an aSAH and 2) preparation of a treatment plan as soon as a patient is transported from another hospital. Direct transportation to the treatment center of aSAH patients can be optimized by education of general practitioners and ambulance employees in order to increase the awareness for SAH[25], or by the presence of a CT-unit in the ambulance, which shortens the time to diagnosis and treatment in ischemic stroke[26]. Additional education has shown to improve the delay to presentation in patients with acute ischemic stroke[25,27], and easy assessment instruments have proven their efficiency in ischemic stroke care[28–30]. A reduction in our delay to treatment after diagnosis could be realized by improving the in-hospital logistics for ultra-early treatment as effectuated in the treatment of ischemic stroke[27,31,32]. This means that especially more attention is given to emergency aneurysm treatment in transferred patients and prevention of postponement of aneurysm obliteration when patients are admitted at a later time point in the day, i.e. aneurysm treatment in evening hours and at night as well.

This study has some limitations. First, our data are based on a single center with the Dutch emergency care system and extrapolation of these data may be difficult, as time intervals to treatment appear to be related to the type of center and country[33]. Second, the time of initial hemorrhage was approximated in almost half of the patients. To reduce the bias herein, approximation occurred in a standardized way by three authors independently and only in those cases where the moment of hemorrhage was linked to a specific event during the day. If there was any uncertainty about the time point, it was stated as irretrievable and excluded from analysis. Although we weren't able to perform a sensitivity analysis on these data, we estimate to have an inaccuracy of just several hours. Finally, the mRS scores have to be interpreted with care, because they were based on outpatient clinical records and rehabilitation letters at different time intervals after the hemorrhage with a wide range, owing to the retrospective study design. However, the median mRS evaluation time of four months after hemorrhage is comparable with the outcome assessment at three months, which is often used in aSAH studies.

In conclusion, a delay in aneurysm treatment is caused by presentation at a referring hospital instead of primarily at a treatment center but is not solely related to the delay of the transport itself. Admission to the treatment center later in the day also contributes to delay, putting patients further at risk for a rebleed. Although the

intervals between initial hemorrhage, diagnosis and start of treatment of patients suffering aSAH were short, there is still room for improvement to optimize ultra-early aneurysm treatment. Immediate and direct transport to a treatment center, and optimization of the in-hospital logistics for ultra-early aneurysm treatment, following the 'time-is-brain' concept so successfully adopted in the treatment of ischemic stroke, especially for patients who are transferred from a referring hospital or are admitted later in the day, might lead to an improved ultra-early treatment. It still needs to be established whether such ultra-early treatment improves functional outcome.

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CHAPTER 3:

Clinical and laboratory characteristics for the diagnosis of bacterial ventriculitis after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Purpose The diagnosis of nosocomial bacterial ventriculitis in patients with subarachnoid hemorrhage (SAH) can be challenging.

Methods We performed a retrospective study on the diagnostic accuracy of clinical and laboratory characteristics for the diagnosis of bacterial ventriculitis in 209 consecutive patients with an aneurysmal SAH admitted in a tertiary referral center from 2008 to 2010. Diagnostic value of clinical characteristics and inflammatory indexes in CSF and blood were determined for three diagnostic categories: 1) no suspicion for bacterial ventriculitis; 2) clinical suspicion for bacterial ventriculitis, defined as initiation of empirical antibiotic treatment for ventriculitis, but negative CSF cultures; and 3) CSF culture-positive bacterial ventriculitis.

Results Empirical antibiotics for suspected ventriculitis was initiated in 48 of 209 (23%) patients. CSF cultures were positive in 11 (5%) patients. Within the group of suspected ventriculitis, only longer duration of CSF drainage and lower CSF red blood cell counts predicted for culture-positivity.
None of the other clinical features or inflammatory indexes in CSF and blood were associated with culture-proven bacterial ventriculitis.

Conclusions Nosocomial bacterial ventriculitis in patients with aneurysmal SAH is often suspected but confirmed by culture in a minority of cases. Improvement of diagnostics for nosocomial bacterial ventriculitis in patients with aneurysmal SAH is needed.

INTRODUCTION

Infections in patients with a subarachnoid hemorrhage (SAH), mainly pneumonia, urinary tract infections, blood stream infections or bacterial ventriculitis, are independently associated with a prolonged stay in the Intensive Care Unit (ICU), a poor outcome and increased mortality[1,2]. Bacterial ventriculitis is reported in 3-29% of SAH patients[2–6], and is strongly associated with the placement of CSF (cerebrospinal fluid) catheters[5,7]. Although infections and fever after SAH have been studied, which includes ventriculitis, no specific study has paid attention specifically and solely to suspected bacterial ventriculitis in this subgroup[1,3,6,8]. In studies on external catheter-related bacterial ventriculitis subgroup analyses specifically for SAH patients have not been performed[9–16]. Although the incidence of external catheter-related bacterial ventriculitis is not expected to be different in other brain injury patients, the clinical symptoms of SAH closely resemble those of bacterial ventriculitis and can thus influence the clinical diagnosis of a bacterial ventriculitis.

A clinical suspicion of nosocomial bacterial ventriculitis should prompt a diagnostic workup and antimicrobial therapy[7]. The diagnostic workup in these patients typically consists of neuroimaging, cerebrospinal fluid analysis (cell counts, Gram's staining, cultures, biochemical tests for glucose and protein), and cultures of blood. The interpretation of the numbers of white cells in cerebrospinal fluid is especially problematic in patients who have bacterial ventriculitis that develops after intraventricular and subarachnoid hemorrhage; although a formula has been proposed for interpretation[12], the diagnostic accuracy is unknown. The diagnosis of nosocomial bacterial ventriculitis is made on the basis of the results of a cerebrospinal fluid culture, of which the results can be false negative. We performed a retrospective cohort study to investigate the diagnostic accuracy of clinical and laboratory characteristics in bacterial ventriculitis after SAH.

MATERIAL AND METHODS

Participants

The Academic Medical Center (AMC) in Amsterdam (The Netherlands) acts as a tertiary referral center for patients with an aneurysmal SAH in a region of approximately 1.3 million people. Consecutive patients admitted with an aneurysmal SAH were included in this study. These patients were collected from a prospectively kept database of all SAH patients admitted in the AMC. There was no objection of the

Medical Ethics Committee of the AMC to perform this study. Patients were excluded if there was no clinical data available (for example due to early referral to another hospital). Clinical records, from the electronic patient chart, were retrospectively examined. World Federation of Neurosurgical Societies (WFNS) grade, Fisher grade, and length of stay were documented. WFNS grade is a five category (I-V) neurological grading scale based upon the Glasgow Coma Score (GCS) in which a higher score indicates a worse clinical condition[17]. Grades were categorized as a dichotomous variable: good (I-III) and poor (IV-V) grade. The Fisher grade is a four-point scale for classification of the amount of extravasated blood on the initial CT-scan (grade 1: no visible hematoma, grade 4: intraventricular or intracerebral hematoma)[18]. Grades were dichotomized into good (Fisher grade 1-3) and poor (Fisher grade 4) grades. Treatment procedures (i.e. coiling, surgical clipping, decompressive craniotomy), catheter placement (external ventricular, lumbar or cisternal catheter), number of catheters and duration of drainage were documented.

Placement and maintenance of the external ventricular and lumbar catheters was performed according to a standardized protocol to minimize the risk of infection[19]. External ventricular catheter placement was performed under sterile circumstances in the operating theatre. Standard external ventricular catheters without antibiotic or silver impregnation were used. The external ventricular catheters were tunneled subcutaneously for at least 5 centimeters. External lumbar catheters were placed at bedside under sterile conditions and also tunneled subcutaneously. In most patients who underwent a craniotomy for surgical clipping of an aneurysm, a cisternal catheter was placed for postoperative CSF drainage during five days. All types of catheters were tunneled subcutaneously. In all procedures, patients received prophylactic antibiotics at least 30 minutes before the start of the surgery: ceftriaxon 1000mg for an external ventricular catheter or a craniotomy, flucloxacillin 1000mg for an external lumbar catheter. The catheters were attended to according to a standardized nursing protocol. No routine microbiological or chemical tests of CSF were taken. External ventricular or lumbar catheters were not routinely changed, they were only changed if there was a dysfunction or if there was an intractable infection.

Selective decontamination of the digestive tract (SDD) was given to all patients in the ICU who were expected to be ventilator-dependent for at least two days. SDD was used as prevention of secondary colonization of patients with gram-negative bacteria in order to reduce mortality[20]. It consisted of Orabase (Polymyxin E 100mg,

Tobramycin 80mg, Amphotericin B 500mg), four times daily orally and intravenous Cefotaxim 3g/24hrs continuously during four days.

Bacterial ventriculitis and diagnostic testing

Bacterial ventriculitis was suspected in SAH patients if they experienced a (new) period of fever (see below for definition) and/or altered mental status and/or (new) nuchal rigidity. Other causes of infection were excluded by performing blood, bronchial and urinary cultures, plain chest X-rays and physical examination. Other causes of an altered mental status, like hydrocephalus or cerebral ischemia, were excluded by performing a plain CT scan.

Clinical records were evaluated to identify patients who were treated for bacterial ventriculitis. If antibiotics were started specifically for ventriculitis, this patient was defined as 'clinically suspected bacterial ventriculitis'. All patients who were started on these antibiotics were included irrespective if they underwent transcranial surgery or had an external ventricular or lumbar catheter placed. Data from the chemical analyses of blood (C-reactive protein (mg/L), white blood cell count (10E9/L) and glucose levels (mmol/L)) and CSF (red blood cells (cells/µL), white blood cell count (cells/µL), protein (g/L) and glucose levels (mmol/L)) and microbiological analyses of CSF were collected. CSF was collected at the time of clinical suspicion of a bacterial ventriculitis from the external ventricular or lumbar catheter in place. If there was no CSF catheter in place a lumbar puncture was performed. Bacterial ventriculitis was defined by a positive CSF culture for bacteria; however, if cultures revealed *Staphylococcus epidermidis* two consecutive positive cultures were need to rule out contamination.

Of all patients, the daily maximum temperature (T_{max}) was collected. Fever was identified as a $T_{max} \geq 38.5$ ˚C. For the calculation of the T_{max} in patients with suspected bacterial ventriculitis the T_{max} until, and including, the day the clinical suspicion of bacterial ventriculitis rose (see definition of bacterial ventriculitis) was used. This was done in order to exclude the days after the (suspected) bacterial ventriculitis, which are not relevant for comparison. For the patients not suspected of bacterial ventriculitis the T_{max} during the whole admission period was used. The number of fever days was defined as the sum of days with a $T_{max} \geq 38.5$ ˚C during the total period of hospitalization. The percentage of fever days was determined by dividing the amount of fever days by the total amount of days when a temperature was taken during the total hospitalization period.

Patients were divided into three groups: 1) no suspicion for bacterial ventriculitis; 2) clinical suspicion for bacterial ventriculitis, defined as initiation of empirical antibiotic treatment aimed specifically at bacterial ventriculitis, but negative CSF cultures; and 3) CSF culture-positive bacterial ventriculitis. Antibiotic regimen for bacterial ventriculitis consisted of ceftriaxon 2 grams twice a day plus vancomycin 2 grams twice a day, or ceftazidim 2 grams three times a day plus vancomycine 2 grams twice a day if an external CSF catheter was in place. Antibiotics were discontinued when the results of the CSF culture were negative (usually after 72 hours)[6]. The antibiotic regimen was continued for two weeks if CSF cultures were positive.

To define a possible effect of SDD on the occurrence of bacterial ventriculitis and on the results of the CSF cultures, patients with suspected bacterial ventriculitis were divided into four groups: CSF culture-negative ventriculitis patients who receive SDD (group 1) or who do not receive SDD (group 2), and patients who have a CSF culture-positive bacterial ventriculitis who do (group 3) or do not receive (group 4) SDD.

Statistical methods

The obtained data were analyzed using Statistical Package for the Social Sciences 16.0 Software (IBM SPSS 19.0). Categorical variables were tested using a χ^2 or Fisher's exact test. Continuous variables were tested with the Kolmogorov-Smirnov test for normal distribution. Normally distributed continuous variables are represented as a mean with a 95% confidence interval (CI), continuous variables which are not normally distributed are represented as a median with a 95% confidence interval (CI). Normally distributed variables were tested with the Student's t-test (two group comparison) or a one-way ANOVA with Bonferroni post-hoc analysis (multiple group comparison). Data that were not normally distributed were tested with the Mann-Whitney U test (two group comparison) or Kruskall-Wallis test (multiple group comparison). Values of $p < 0.05$ were considered as statistically significant.

RESULTS

Participants

Between November 1st 2008 and October 31st 2010, 211 consecutive patients with an aneurysmal SAH were admitted. Two patients were excluded, leaving 209 patients for further analysis. All patients were initially admitted to the ICU. The clinical characteristics of 209 patients are presented in table 1. Of the 149 coiled patients 69

(46%) had an external ventricular or lumbar catheter placed during the admission period, in contrast with 26 (90%) of the 29 clipped patients.

Table 1. Clinical characteristics of 209 patients with an aneurysmal subarachnoid hemorrhage

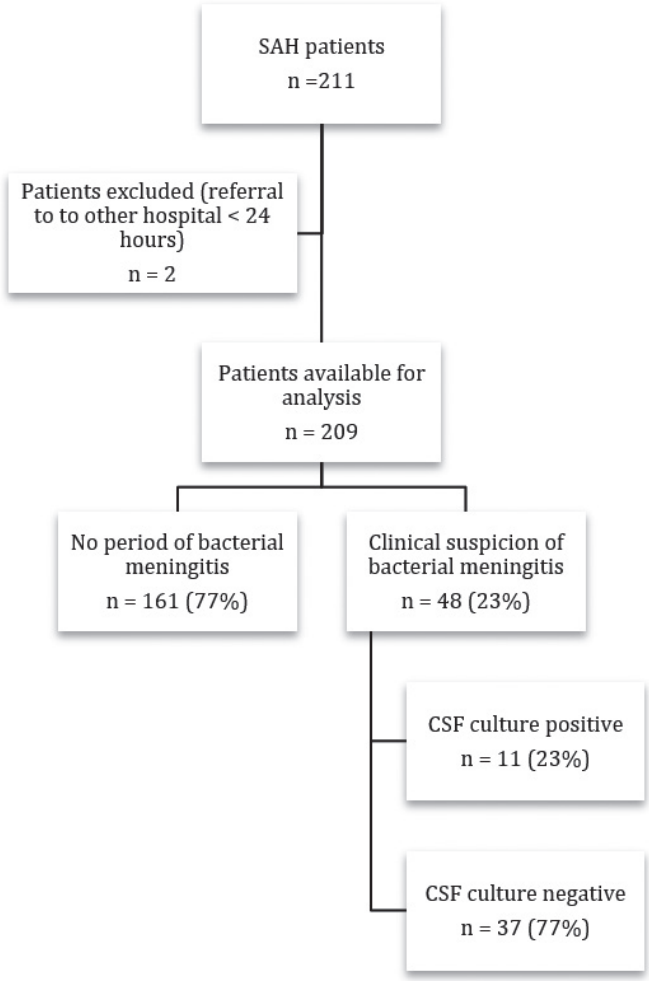
Patients, n	209
Mean age, years (95% CI)	54.8 (53.0-56.6)
Female, n (%)	130 (62)
Treatment, n (%)	
No aneurysm treatment	31 (15)
Coiling	149 (71)
Clipping	29 (14)
Decompressive craniectomy, n (%)	15 (7)
External ventricular catheter, n (%)	77 (37)
External lumbar catheter, n (%)	32 (15)
Cisternal catheter, n (%)	19 (9)
Lumbar puncture, n (%)	42 (25)
No CSF drainage, n (%)	108 (52)
WFNS grade, n (%)	
I-III	122 (58)
IV-V	87 (42)
Fisher grade, n (%)	
1-3	122 (58)
4	87 (42)

WFNS World Federation of Neurosurgical Societies; *CSF* cerebrospinal fluid.

Forty-eight (23%) patients were treated with antibiotics for a clinical suspicion of bacterial ventriculitis and CSF cultures were positive in only 11 of these 48 patients (23%; Figure 1; table 2).

Bacteria cultured from CSF were *Staphylococcus epidermidis* (n=8), *Enterococcus* species (n=2), and Staphylococcus *aureus* (n=1). One patient had two episodes of suspected ventriculitis during one hospitalization (14 days between episodes) but both episodes remained culture-negative.

Figure 1. Flow chart regarding SAH patients with a clinical suspicion of bacterial meningitis



SAH Subarachnoid hemorrhage
CSF Cerebrospinal fluid

Table 2. Clinical characteristics of three patient groups according to presence of bacterial ventriculitis

Characteristics			
Clinical	**No suspected ventriculitis**	**Suspected ventriculitis**	**Suspected ventriculitis**
CSF culture	**negative**	**negative**	**positive**
Patients, n	161	37	11
Mean age, years (95% CI)†	55.0 (52.9-57.1)	55.2 (51.4-59.0)	50.3 (40.8-59.7)
Female, n (%)	102 (63)	21 (57)	7 (64)
Median duration of hospitalization, days (95% CI)‡	12.0 (11.0-13.0)[a]	23.0 (20.0-33.0)	34.0 (16.0-54.0)
WFNS grade, n (%)			
I–III	102 (63)[b]	17 (46)	3 (27)
IV-V	59 (37)[b]	20 (54)	8 (73)
Fisher grade, n (%)			
1-3	99 (62)	18 (49)	5 (46)
4	62 (38)	19 (51)	6 (54)
Treatment, n (%)			
No aneurysm treatment	30 (19)[b]	1 (3)	0 (0)
Coiling	111 (69)[b]	26 (70)	11 (100)
Clipping	19 (12)[b]	10 (27)	0 (0)
Decompressive craniectomy, n (%)	12 (8)	3 (8)	0 (0)
External ventricular catheter, n (%)	44 (27)[a]	24 (65)	9 (82)
External lumbar catheter, n (%)	13 (8)[a]	12 (32)	7 (64)
Cisternal catheter, n (%)	13 (8)[a]	6 (16)	0 (0)
Lumbar puncture, n (%)	50 (31)[a]	3 (5)	0 (0)
No CSF drainage, n (%)	98 (61)[a]	3 (8)	0 (0)
Median duration external CSF drainage, days (95% CI)‡	6.0 (4.0-10.0)[a]	14.0 (8.0-17.0)[c]	19.0 (12.0-41.0)
Median duration of CSF drainage (days) of the external catheter preceding clinical suspicion of BM (95% CI)‡	-	4.0 (4.0-6.0)[c]	14.0 (4.0-19.0)
SDD, n (%)	45 (28)[d]	20 (54)	5 (46)

WFNS World Federation of Neurosurgical Societies; *CSF* cerebrospinal fluid; *SDD* Selective decontamination of the digestive tract. †one-way ANOVA. ‡Kruskal-Wallis.

[a]significant difference ($p < 0.05$) between no suspected ventriculitis, and CSF culture-negative ventriculitis and CSF culture-positive bacterial ventriculitis.

[b]significant difference ($p < 0.05$) between no suspected ventriculitis and CSF culture-positive bacterial ventriculitis.

[c]significant difference ($p < 0.05$) between culture-negative ventriculitis and CSF culture-positive bacterial ventriculitis.

[d]significant difference ($p < 0.05$) between no ventriculitis and culture-negative bacterial ventriculitis.

Patients with bacterial ventriculitis were admitted in worse clinical condition, as reflected by higher WFNS grade at presentation, in comparison with patients without bacterial ventriculitis (median grade 4 vs. 2; p = 0.03). In total 108 (52%) patients received a CSF catheter: 75 patients (36%) had primarily an external ventricular catheter placed, 16 (8%) an external lumbar catheter and 17 (8%) a cisternal catheter as the first form of CSF drainage. Seventy-nine patients (38%) had only one drain (either ventricular or lumbar) placed during hospitalization, 21 had 2 external catheters (10%) during admission, 7 patients (3%) had 3 and 1 patient (1%) even had 4 consecutive external catheters placed during hospitalization. Placement of external CSF catheters was associated with higher WFNS grades on admission (p < 0.001). All patients who had a culture proven ventriculitis had one or more external ventricular catheters placed before they developed a bacterial ventriculitis. Of the 37 suspected patients in whom the CSF cultures came back negative 3 (8%) never had an external CSF catheter. Among patients with an external CSF catheter placed, the number of days with a catheter in situ was associated with the diagnosis of suspected ventriculitis (median 14 days (8-17)) and culture-proven bacterial ventriculitis (median 19 days (12-41); table 2). The length of hospitalization was less with the diagnosis of suspected ventriculitis (median 23 days (20-33)) than with a culture-proven bacterial ventriculitis (median 34 days (16-54); table 2).

Clinical symptoms and chemical analyses

The clinical symptoms and laboratory features in blood and CSF are presented in table 3. Patients without ventriculitis showed significantly lower median temperatures and less fever days than both other groups (p < 0.05). There were no significant differences however, in median temperatures and the median amount of fever days (both absolute and relative) between patients with CSF culture-positive bacterial ventriculitis and CSF culture-negative ventriculitis. The RBC count in CSF was significantly higher in patients with CSF culture-negative ventriculitis (102900 cells/µL (33600-177000)) than in patients with CSF culture-positive bacterial ventriculitis (6300 cells/µL (1200-7168000); p = 0.01) (table 3). Other clinical symptoms and laboratory features did not significantly differ between the groups.

Selective decontamination of the digestive tract and antibiotics

SDD was administered in 34% of all patients. Patients treated for (suspected) bacterial ventriculitis received SDD more frequently than patients without bacterial ventriculitis, however, this difference was only significant between patients with culture-negative ventriculitis and patients without ventriculitis (p < 0.01). There

was no significant difference between CSF culture-positive bacterial ventriculitis and CSF culture-negative ventriculitis (p = 0.74) (table 2).

Table 3. Clinical symptoms, cerebrospinal fluid and blood characteristics according to the presence of a positive CSF culture.

Characteristics			
Clinical	**No suspected ventriculitis**	**Suspected ventriculitis**	**Suspected ventriculitis**
CSF culture	**negative**	**negative**	**positive**
Patients, n	161	37	11
Nuchal rigidity, n (%),‡	-	11 (100)	6 (67)
Altered mental status, n (%)	-	9 (24)	4 (36)
Number of patients with > 38.5 °C, n (%)	67 (42)[a]	32 (87)	10 (91)
*Median Tmax (95% CI)†**	37.5 (37.5-38.0)[a]	37.7 (37.5-38.0)	37.6 (37.3-38.3)
Median amount of fever days (95% CI)†#	0.0 (0.0-1.0)[a]	5.0 (2.0-7.0)	3.0 (1.0-11.0)
Median relative amount of fever days, % (95% CI)†#	0.0 (0.0-3.7)[a]	19.1 (11.1-32.4)	16.7 (4.0-47.1)
CSF			
Median RBC, cells/µL (95% CI)†	-	102900.0 (33600.0-177000.0)[b]	6300.0 (1200.0-7168000.0)
Median WBC, cells/µL (95% CI)†	-	1722.0 (1191.0-2430.0)	3225.0 (489.0-15595.0)
Median protein, g/L (95% CI)†	-	1.0 (0.7-1.5)	1.2 (0.6-2.9)
Mean glucose, mmol/L (95% CI)¥	-	3.4 (2.9-3.8)	2.7 (1.8-3.6)
Serum			
Median CRP, mg/L (95% CI)†	-	33.3 (20.5-89.7)	40.9 (11.0-89.7)
Median WBC, 10E9/L (95% CI)¥	-	12.7 (10.1-14.8)	15.1 (11.4-18.8)

CSF cerebrospinal fluid; *RBC* red blood cells; *WBC* white blood cells; *CRP* C-reactive protein.
†Mann-Whitney U. ¥ Student's t-test.
‡nuchal rigidity was documented in 17 patients. Represented here is the percentage of patients in whom this was documented.
*measured until and including the day of clinical suspicion of bacterial ventriculitis. #measured during the whole period of hospitalization.
[a]significant difference (p < 0.05) between no suspected ventriculitis and CSF culture-negative ventriculitis, and between no suspected ventriculitis and CSF culture-positive bacterial ventriculitis.
[b]significant difference (p = 0.01) between CSF culture-negative BM and CSF culture-positive BM .

We found no significant differences in clinical characteristics, CSF features, or in duration of drainage, between CSF culture-negative ventriculitis with or without SDD and patients with CSF culture-positive bacterial ventriculitis with or without SDD. The CRP in blood was significantly (p = 0.01) lower (median 17.2 mg/L (1.6-40.9) for patients with a CSF culture-positive bacterial ventriculitis using SDD than for patients with CSF culture-positive bacterial ventriculitis without SDD (median 69.1 mg/L (14.1-168.3)). The WBC count in blood was significantly higher for patients with CSF culture-positive bacterial ventriculitis with SDD (mean 15.9 10E9/L (13.6-18.2)) compared to patients with CSF culture-positive bacterial ventriculitis without SDD (mean 14.7 10E9/L (10.7-18.7)) (p = 0.02). The CSF cultures of patients with CSF culture-positive bacterial ventriculitis yielded similar results for patients with or without SDD: Staphylococcus epidermidis in 4 of 6 patients without SDD, and in 4 of 5 patients with SDD.

Four of 11 (36%) patients with culture-positive bacterial ventriculitis and 7 of 39 (18%) patients with a culture negative ventriculitis received antibiotics for another cause of infection before ventriculitis treatment (p = 0.23). None of the patients with CSF culture-positive bacterial ventriculitis and 12 of the 39 (31%) patients with CSF culture-negative ventriculitis received antibiotics for another infection after discontinuation of antibiotic treatment (p = 0.05).

DISCUSSION

This study shows that almost a quarter of all patients admitted with an aneurysmal subarachnoid hemorrhage were treated with antibiotics for a clinical suspicion of bacterial ventriculitis, but that only in a small minority of these patients the CSF culture proved positive. A clinical suspicion of nosocomial bacterial ventriculitis should prompt a diagnostic workup and antimicrobial therapy. Our data show that clinical signs of ventriculitis are nonspecific and difficult to recognize in SAH patients who are sedated, who have recently undergone neurosurgery, or have a sterile inflammatory response in the CSF due to the SAH. Therefore, improvement of diagnostics for nosocomial bacterial ventriculitis in patients with aneurysmal SAH are needed to improve patients care and to reduce the administration of antibiotics, in order to lower the risk of antibiotic resistance development, and concomitantly to decrease health care costs.

The clinical symptoms of SAH, including headache, nuchal rigidity and altered mental status, closely resemble those of bacterial ventriculitis. These symptoms are

thus non-specific and probably not useful to distinguish between both conditions. Fever, the most consistently reported feature in bacterial ventriculitis, occurs in 40% of the patients after SAH with or without an infection[21–24]. The cell count in CSF may be helpful but has a low sensitivity and specificity[7]. The interpretation of white blood cells (WBC) in CSF is especially problematic in patients who develop bacterial ventriculitis after SAH as the presence of red blood cells (RBC) in CSF in itself causes an aseptic ventriculitis[9,10,12,14]. The proposed cell index for external ventricular drainage-related ventriculitis in patients with intraventricular hemorrhage was not confirmed in subsequent series[12].

In the absence of better discriminative tests, treatment is usually initiated on first suspicion. Because nosocomial bacterial ventriculitis is associated with high mortality and morbidity[10,14,25,26]. With this treatment strategy we aimed in this study that as few as possible bacterial ventriculitis patients were missed and as much as possible were treated, thus reducing the morbidity and mortality. Furthermore, the antibiotics were discontinued as soon as the cultures come back negative, which was normally after three days. Although the CSF culture (the most validated test for bacterial meningitis and ventriculitis) was used as gold standard for diagnosis, it is known that false negative tests may occur[21,27,28]. In the population under study this could be further enhanced by the routine use of selective decontamination of the digestive tract in patients who were expected to be ventilator-dependent for at least two days. Patients who were treated for a (suspected) bacterial ventriculitis were more often in a worse clinical condition, hence the expectation to be ventilator-dependent. These poor condition patients are also the patients who are more prone to develop a bacterial ventriculitis[2]. Prophylactic antibiotics may mask a positive CSF culture leading to a negative CSF culture in patients with true bacterial ventriculitis. However, only one of the patients clinically suspected of bacterial ventriculitis in whom antibiotics were discontinued after a negative CSF culture experienced a second period of clinically suspected and culture-positive bacterial ventriculitis. In this patient, the first suspicion in retrospect was low. Fever reoccurred five days after discontinuation of the antibiotics for the first suspicion and was preceded by a drain blockage for which surgical revision was necessary.

CSF drainage procedures are common after an SAH and a longer duration of external drainage makes patients more susceptible to bacterial ventriculitis[7,29,30]. Not surprisingly, duration was significantly longer in patients with CSF culture-

positive bacterial ventriculitis than in patients with CSF culture-negative bacterial ventriculitis. This is in concurrence with what is reported in the literature[7,9,15,16].

Three patients had a clinical suspicion after a lumbar puncture as sole procedure and 3 did not even had any procedure (shunting, surgery or lumbar puncture) at all. Despite this fact they did show clinical signs of bacterial ventriculitis. Emphasizing the difficulty in clinical diagnosis.

We found no specific CSF features that distinguish in the early diagnosis of ventriculitis after SAH, although the CSF red blood cell (RBC) count was higher in patients with CSF culture-negative bacterial ventriculitis than in patients with CSF culture-positive bacterial ventriculitis. The influx of RBCs in the CSF after SAH causes CSF disturbances, these have been shown to have a poor discriminatory value[10,12,31–33]. Other substrates, such as CSF lactate, cytokine levels, and serum procalcitonin are also disturbed after SAH. Although procalcitonin has been shown to be able to discriminate between a systemic inflammatory response syndrome and a systemic infection[34], the value to differentiate between aseptic and bacterial ventriculitis of this and other substrates is limited[33–38]. Polymerase chain reaction of the CSF for the detection of bacterial pathogens has been shown to have a low sensitivity in patients with an external catheter-related bacterial ventriculitis and patients with aseptic ventriculitis after surgery, but assays are getting more sensitive[39–42].

S. epidermidis was the most common pathogen found in the CSF cultures, as in other studies on external catheter-related bacterial ventriculitis[7,9,10,14–16,43]. However, the frequency of *S. aureus* as causative pathogen was lower than described in the literature, possibly the result of selective SDD which is aimed at reducing infection with *S. Aureus*[19,44].

Limitations of this study are its retrospective nature and the small sample of patients with CSF culture-positive bacterial ventriculitis. Data were collected from clinical records, and underreporting of clinical suspicion and features may have biased the results. However, patients were only categorized as CSF culture-negative ventriculitis if antibiotics were started for this suspicion, which is a well-defined criterion with a computerized medication prescription system used in our facility. The choice of antibiotics is also quite specific and thus readily traceable to a tentative diagnosis of bacterial ventriculitis.

In this retrospective series of SAH patients, nosocomial bacterial ventriculitis is often suspected but confirmed by culture in a minority of cases. The clinical signs of ventriculitis are nonspecific and difficult to recognize in SAH patients. Improvement of diagnostics for nosocomial bacterial ventriculitis in patients with aneurysmal SAH is needed.

CONFLICTS OF INTEREST STATEMENT

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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CHAPTER 4:

Why do poor-grade subarachnoid hemorrhage patients die?

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ABSTRACT

Background Poor-grade subarachnoid hemorrhage (SAH) is associated with a high case fatality, either in the acute phase or in the later stages. The exact causes of demise in these patients are unknown.

Methods We performed a retrospective study in all consecutive SAH patients with a World Federation of Neurosurgical Societies (WFNS) grade IV and V on admission, between 2009 and 2013 in two tertiary referral centers in Amsterdam (the Netherlands) and Toronto (Canada) and who died during their hospital stay.

Results Of a total of 357 patients, 152 (43%) died, amongst whom 87 (24%) who did not undergo aneurysm treatment. The median interval to death was three days (IQR 1-12) after initial hemorrhage. The major cause of death in both centers was withdrawal of life support (in total 107 (71%) patients; 74 (79%) of 94 in Amsterdam and 33 (58%) of 58 patients in Toronto ($p < 0.01$)), followed by brain death in 23 (15%): 16 (28%) of 58 in Amsterdam versus 7 (7%) of 94 in Toronto, $p < 0.01$]. The remaining causes of demise represented less than 15%.

Conclusions The decision to withdraw life support is the major reason of demise in poor-grade SAH patients in an overwhelming majority of patients. The exact reasons for withdrawal of life support, besides cultural and referral differences, remain undetermined. Insight into the reasons of demise should be prospectively studied in order to improve the care clinical outcome of poor-grade SAH patients.

INTRODUCTION

Patients with subarachnoid hemorrhage (SAH) present in a poor clinical condition in about 30% [1–3]. The in-hospital mortality of these patients exceeds 50%[4–6], in the acute phase due to the direct impact of the SAH[7–10], in the later stages due to secondary medical complications, or withdrawal of life support (WOLS)[10,11].

Historically, patients in a poor clinical condition are treated with observation in intensive care, awaiting clinical improvement before initiating aneurysm treatment[12]. However, during this interval, poor-grade patients are at a high risk of a rebleed and hydrocephalus, leaving them susceptible to a worsening of their condition and subsequently death. More recently, a more expeditious approach regarding poor-grade SAH patients has been advocated, with early aneurysm treatment and urgent external ventricular drainage. This strategy leads to a higher percentage of good (i.e. Glasgow Outcome Scale scores 4-5 at three months) outcome in poor-grade patients[5,11,13–15]. Despite this more aggressive treatment, a significant number of poor-grade patients still die during admission, raising the question of how case-fatality may be reduced.

To obtain a better insight into the causes of death in poor-grade SAH patients, we studied a double-center cohort in two university hospitals in Canada and the Netherlands.

MATERIAL AND METHODS

Patients

Poor-grade [World Federation of Neurosurgical Societies (WFNS) grade IV and V] aneurysmal SAH patients, consecutively admitted between 2009 and 2013 in two academic SAH treatment centers were included in this cohort. The WFNS grade is a five-point neurological grading scale based upon the Glasgow Coma Scale (GCS), in which a higher score indicates a worse clinical condition[16]. A WFNS grade IV and V were defined as a poor-grade SAH and included in this study. The WFNS grade was determined on admission at the treatment centers. If the patient was transferred from a referring center intubated and/or under sedation, the last known grade before the start of sedation was used. Patients were included if they had an aneurysmal SAH distribution pattern of blood on the initial CT-scan. Patients with a perimesencephalic bleeding pattern were excluded. No other in- or exclusion criteria were applied. The Amsterdam University Medical Centers, location AMC,

(AUMC in Amsterdam, the Netherlands), is an academic teaching center affiliated with the University of Amsterdam and tertiary referral center for SAH patients in the Amsterdam metropolitan area, with a total population of approximately 2.5 million people. It admits around 150 SAH patients per year. St. Michael's Hospital (SMH) in Toronto (Canada) is also an academic teaching center, affiliated with the University of Toronto. It is a tertiary referral center for aneurysmal SAH patients with approximately 150 admissions of patients with an aneurysmal SAH per year.

Because this was an observational study, formal approval was waived by the institutional ethical review board of our hospital and patient consent was not required.

Patient management

All patients were admitted to the Intensive Care Unit. In both centers patients were managed according to the institutional protocol[17], which follow the international guidelines on SAH care[18].

Data collection

Patients were selected from both a retrospective (2008-2011), as well as a prospective (2011 and onwards) database at the AUMC, and from a retrospective database at SMH. Patient charts were retrospectively searched for missing data. Data on demographic characteristics, WFNS grade on admission (grade IV and V), modified Fisher grade, intracerebral hemorrhage, epileptic seizures at presentation, recurrent hemorrhages, presence of hydrocephalus (on plain CT-scan) during the admission period, delayed cerebral ischemia (DCI), interventions (i.e. coiling, surgical clipping and placement of an external ventricular drain (EVD) or ventriculoperitoneal shunt (VPS) and in-hospital mortality was collected.

The modified Fisher grade is a four-point scale for classification of the amount of extravasated blood on the initial CT-scan. It ranges from no visible hematoma (grade 0) till thick intraventricular hematoma with bilateral intraventricular hematoma (grade 4)[19]. Epileptic seizures on admission were scored if this was suspected at the ictus or shortly afterwards. Rebleeding was defined as a new bleeding from the causative aneurysm after the initial bleeding. This was determined as an increase of blood on a plain CT-scan of the head, or when a patient experienced an outflow of fresh blood from their EVD. Hydrocephalus was scored as marked ventricular dilatation on a plain CT-scan, read by an experienced neuroradiologist. DCI was

defined as a new focal neurological deficit (motor or speech) or a decrease of two points or more on the GCS, for at least one hour, that could not be attributed to other causes such as hydrocephalus, electrolyte or metabolic disturbances, rebleeding or post-treatment complications or infections[20].

The major cause of death was extracted from the patient charts (by J.H. in the AUMC, by A.L.O.M. in the SMH). For the deceased patients, the causes of death were categorized as followed:

(a) Withdrawal of life support - withholding or withdrawal of life support were defined as the "processes by which various medical interventions are either not given to, or are taken away from, patients with the expectation that they will die as a result"[21];
(b) Brain death by neurological criteria defined according to the Canadian Neurological Determination of Death[22], and the Brain Death Protocol by the Health Council of the Netherlands[23]. The criteria used for determining brain death are similar in both countries;
(c) Cardiopulmonary causes, including cardiopulmonary arrest or circulatory arrest, neurogenic pulmonary edema and acute respiratory distress syndrome (ARDS), SAH-induced myocardial dysfunction (e.g. Tako-Tsubo cardiomyopathy), life-threatening arrhythmias[24];
(d) Aneurysm rebleeding;
(e) Increased intracranial pressure (ICP) refractory to medical treatment and/or decompressive craniectomy, leading to brain stem herniation;
(f) Other extracranial causes, such as systemic infections.

Some categories will overlap in a selection of patients; in those cases the major contributing factor leading to the demise was used. The number of days from initial hemorrhage till the demise and the length of hospital stay were calculated.

Statistical analyses

Categorical variables were tested using a χ^2 or Fisher exact test. Odds ratios are represented with a 95% confidence interval (CI). Continuous variables were tested with the Kolmogorov-Smirnov test for normal distribution. Normally distributed continuous variables were tested with the Student's t-test and represented as a mean with a standard deviation (SD), continuous variables which were not normally distributed were tested with Mann-Whitney U and represented as a median with an interquartile range (IQR

25%-75%). Data were analyzed using Statistical Package for the Social Sciences Software (IBM SPSS 21.0). Values of $p<0.05$ were considered statistically significant.

RESULTS

During the study period a total of 357 patients with poor grade SAH was admitted: 178 to the AUMC, 179 to the SMH. Baseline characteristics are shown in table 1. A total of 152 (43%) patients died during admission, of whom 87 (24% of 357 patients) did not undergo aneurysm treatment. According to WFNS grade, a total of 34 (25% of 134) WFNS IV patients, versus 118 (53% of 223) WFNS V patients died, respectively (OR (95% CI) 0.30 (0.19-0.48)).

Table 1. Baseline characteristics

	N (%)
Total	357 (100)
Male	125 (35)
WFNS 5	223 (63)
Median GCS at admission (IQR)	5 (3-8)
Median age (IQR)	55 (48-64)
Modified Fisher Scale	
0	2 (1)
1	15 (4)
2	22 (6)
3	148 (42)
4	169 (47)
missing	1 (1)
Median days till demise after SAH (IQR)	3 (1-12)
Intracerebral hemorrhage	122 (34)
Treatment	
Coiling	192 (54)
Clipping	67 (19)
None	89 (25)
External ventricular shunt	259 (73)
Ventriculoperitoneal shunt	51 (14)
Craniectomy	53 (15)

Data are presented as n (%), unless otherwise stated.

Causes of death

Withdrawal of life support (WOLS) was the major cause of death in 107 (71%) of the 152 deceased patients, followed by brain death in 23 (15%). The remaining causes of demise represented less than 15% (table 2). Of the five patients, whose death was directly related to a recurrent hemorrhage, one had an untreated aneurysm, and four underwent aneurysm treatment. Of these four, three patients had a rebleed during the coiling procedure, in one this remained unknown. In the patient who had an untreated aneurysm, treatment was technically not possible due to extensive vasospasms on the angiogram. Four patients died of other extracranial causes, all of them underwent aneurysm treatment. The extracranial cause was a complicated pneumonia in one patient and septic shock in another, one patient was diagnosed with a disseminated progressive malignancy and one died because of intestinal ischemia associated with prolonged use of noradrenaline.

Table 2. Reasons of demise

	N (%)
Total demised patients	152 (100)
Withdrawal of life support	107 (71)
Brain death	23 (15)
Cardiopulmonary causes	6 (4)
Rebleeding	5 (3)
Refractory elevated ICP	5 (3)
Extracranial other	4 (2)
Unknown	2 (1)

Reasons of demise according to median days to death

The median interval to death was three days (IQR 1-12) after initial hemorrhage. When the reasons of demise were compared within three days after the ictus and after three days, WOLS remained the major cause of death. All patients who died of cardiopulmonary causes died within 3 days after the SAH (OR (95% CI) 11.35 (0.63-207)). All patients who died because of refractory elevated ICP did so within three days, though this was not significant (OR (95% CI) 10.27(0.56-189.1)). Also, more patients died as a result of brain death or extracranial complications, but this was also not significant (table 3).

Treated versus untreated aneurysm

Eighteen (21%) of 87 patients who died without aneurysm treatment were declared brain dead, compared to five (8%) of 65 patients whose aneurysm was treated (OR (95% CI) 3.12 (1.10-8.93)). All six patients who died of cardiopulmonary causes did not have their aneurysm treated (OR (95%) 10.42 (0.58-188.30)). The other causes of demise were not different between the treated and untreated patients (table 4).

Table 3. Reasons of demise according to median days till demise. Data are presented as n (%).

	Within 3 days, N (%)	After 3 days, N (%)	Odds ratio (95% CI)
Total	80 (100)	71 (100)	
*Withdrawal of life support**	50 (63)	56 (80)	0.42 (0.20-0.87)
Brain death	16 (20)	7 (10)	2.25 (0.87-5.84)
Cardiopulmonary causes	6 (8)	0 (0)	11.35 (0.63-207)
Rebleeding	3 (4)	2 (3)	1.32 (0.22-8.17)
Refractory ICP	5 (6)	0 (0)	10.27(0.56-189.1)
Extracranial other	0 (0)	4 (4)	0.12 (0.01-2.36)
Unknown	0 (0)	2 (3)	0.18 (0.01-3.61)

Demise after 3 days is the reference category. *1 patient missing days of demise.

Table 4. Reasons of demise according to aneurysm treatment. Data are presented as n (%).

	No aneurysm treatment, N (%)	Aneurysm treatment, N (%)	Odds ratio (95% CI)
Total	87 (100)	65 (100)	
Withdrawal of life support	58 (67)	49 (75)	0.60 (0.29-1.25)
Brain death	18 (21)	5 (8)	3.12 (1.10-8.93)
Cardiopulmonary causes	6 (7)	0 (0)	10.42 (0.58-188.30)
Rebleeding	1 (1)	4 (6)	0.18 (0.02-1.62)
Refractory ICP	4 (4)	1 (2)	3.10 (0.34-28.18)
Extracranial other	0 (0)	4 (6)	0.10 (0.01-2.00)
Unknown	0 (0)	2 (1)	0.14 (0.01-3.06)

Aneurysm treatment is the reference category.

WFNS IV versus WFNS V

When the reasons of demise were compared for patients graded WFNS IV versus V, no significant differences were found (table 5). Also, in solely WFNS grade

IV patients there were no differences in causes of demise between treated and untreated patients.

Table 5. Reasons of demise according to WFNS IV versus V. Data are presented as n (%).

	WFNS IV, N (%)	WFNS V, N (%)	Odds ratio (95% CI)
Total	34 (100)	118 (100)	
Withdrawal of life support	22 (65)	85 (77)	0.69 (0.31-1.56)
Brain death	5 (15)	18 (15)	0.95 (0.32-2.78)
Cardiopulmonary causes	1 (3)	5 (4)	0.68 (0.08-6.02)
Rebleeding	2 (6)	3 (3)	2.38 (0.38-14.83)
Refractory ICP	1 (3)	4 (3)	0.86 (0.09-7.92)
Extracranial other	2 (6)	2 (2)	7.25 (0.64-85.52)
Unknown	1 (3)	1 (1)	3.52 (0.21-57.72)

WFNS grade V is the reference category.

Amsterdam versus Toronto

More patients were admitted to the AUMC with a WFNS grade V; 121 (54%) of 178 patients versus 102 (46%) of 179 patients in SMH (p= 0.04). Ninety-four (53%) of the 178 patients died in the AUMC versus 58 (32%) of 179 in the SMH (p < 0.01). In both centers WOLS was the most important reason of demise; 74 (79%) of 94 in the AUMC, 33 (58%) of 58 patients in SMH (p < 0.01). Fewer patients died in the AUMC because of brain death [7 (7%) of 94 versus 16 (28%)of 58, p < 0.01]. There were no significant differences in the other reasons of demise.

DISCUSSION

In this cohort of expeditiously treated poor-grade SAH patients, almost half (43%) died during the hospitalization period. The overall main reasons of demise were withdrawal of life support and brain death. The remaining causes of death comprised less than 15% of the patients who died. Of the patients who did not undergo aneurysm treatment, virtually all (87 of 89, (98%) patients) died.

Withdrawal of life support (WOLS) has been shown to be the main cause of death in traumatic brain injury[25] and intracerebral hemorrhage[26,27]. It is most commonly initiated when a patient is expected not to achieve a favorable outcome[21]. The decision to withdraw life support is usually an expert-based decision; there are

very few prognostic tools to accurately predict prognosis. This can lead to nihilism and self-fulfilling prophecies[28] and leaves room for the possibility to withdraw life support too soon. An expeditious approach of poor-grade SAH patients has been shown to lead to an improved outcome[11,15]. If given more time to show recovery, in combination with a more expeditious treatment, patients could then potentially improve to a favorable outcome.

A study by Lantigua et al. showed a general mortality of 18% of patients of all grades[29]. In the subgroup of poor-grade patients, the mortality was 47.5%, which is comparable to our results. In 43% of the patients WOLS was the cause of death. The higher rate of WOLS in our series might be attributable to an earlier decision to stop general treatment, which caused patients to die before they were officially declared brain death, possibly reflecting cultural and religious differences. This has previously also been shown in the study of Lantigua et al. where the decision for WOLS in the US was made with a higher threshold compared to Europe and Canada [29,30]. We found that the decision to withdraw life support was made more frequently in Amsterdam than in Toronto, leading to more patients dying in the Amsterdam group. Possibly there is a lower threshold in Amsterdam to stop further treatment if physicians expect a poor outcome. This higher percentage of WOLS in Amsterdam could also partly be explained by the fact that this group consisted of more WFNS grade V patients. Not only are travelling distances between referral and treatment centers much shorter in the Netherlands than in Canada, federal regulations strictly dictate that SAH patients can only be treated in designated treatment centers. For these reasons there is a lower threshold to accept patients, even in a very poor condition, leading to a higher percentage of WFNS grade V patients in Amsterdam.

The percentage of patients with brain death was 15%, which was lower than the 42% found in the study of Lantigua et al.[29]. This might be due to different definitions of brain death or earlier decisions to withdraw life support. In our study, in the patients treated in the Netherlands, the procedure to determine brain death was only done if a patient was eligible for organ donation and if there was consent (given by the family or by the patient through the nationwide registry). If no organ donation was possible or expected, brain death was not determined. Possibly, some of the patients in whom treatment was discontinued would have become brain death, but it was not diagnosed as such. This could also explain in part the higher percentage of WOLS in the Amsterdam group.

Patients who were not treated for their aneurysm died as a result of brain death more often than treated patients. These patients were probably in a very poor condition, which caused a massive rise in ICP, brain death and cardiopulmonary complications. It seems likely that these events would have contributed to the decision to refrain from treatment of the aneurysm, EVD placement and maximum supportive care. This is supported by the fact that these patients also died more often of cardiopulmonary causes, which can be a sign that patients were not stable enough to proceed to treatment.

In this study only five patients died directly after a rebleed. This number seems low compared to other studies in which recurrent hemorrhage occurs in up to a third of the poor-grade patients[31,32]. This low rate of recurrent hemorrhages can be explained by the fact that nowadays treatment of the aneurysm is initiated as soon as logistically possible[13,33,34]. Because of this earlier treatment the mortality related to recurrent hemorrhages has significantly decreased[35]. On the other hand, the low rate of patients with a recurrent hemorrhage as the reason for demise, can be explained by the fact that in most cases a recurrent hemorrhage will not lead to death directly, but to deterioration in neurological function. This deterioration in neurological function might lead to the decision to WOLS or to determine brain death.

Only a small portion of patients died as a direct result of refractory elevated ICP, suggesting that in most patients the ICP was kept at a level that was acceptable to continue treatment. When a prolonged raised ICP was a reason to withdraw life support, this was allocated as WOLS.

A limitation of this study is its retrospective nature. Although the core data (i.e. patient demographics, patient characteristics upon admission and modified Rankin Scale score on follow-up) were all collected prospectively, other data had to be retrospectively extracted from the patient charts, which depend heavily on the accuracy of physicians' annotations and subsequent interpretation of the researchers. Particularly for the reasons of demise this frequently caused failure to exactly pinpoint the reasons behind the withdrawal of life support, as retrospective retrieval of data is known to be inherently less accurate than prospectively entered data. These exact reasons will be necessary to determine if there are patients in this group for whom further treatment may be worthwhile. We think these exact reasons can be better and more precisely documented in a prospective study.

A major advantage of this study is the relatively high number of patients included with a WFNS grade IV and V in two centers that support early and expeditious treatment of poor-grade SAH patients. Additionally, the availability of databases of centers in two different continents revealed a novel insight into the decision-making process in treatment of poor-grade SAH patients showing that the reason of death in poor-grade SAH patients is different between continents.

It is important to understand the reason of demise in poor-grade SAH patients as this might lead to a better insight into the approach towards these patients. Direct causes of death, such as cardiopulmonary complications, refractory raised ICP or a recurrent hemorrhage, require a completely different treatment than when death is the result of a physician's decision to withdraw treatment based on a presumed poor prognosis. An understanding of this process of withdrawal of life support could lead to a better selection of patients who potentially reach a better outcome and lead a meaningful life. Prospective research needs to be done to understand the decision-making processes in poor-grade SAH patients.

CONCLUSIONS

Not the severity, nor the complications, of SAH per se, but the decision to withdraw life support is the major reason of demise in poor-grade SAH patients in an overwhelming majority of patients. However, the exact reasons for withdrawal of life support, besides cultural and referral differences, remain undetermined. As death caused by either the direct sequelae of the SAH or by withdrawal of support is potentially preventable, an insight into the reasons of demise should be prospectively studied in order to improve the care of poor-grade SAH patients through better patient selection in the future.

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CHAPTER 5:

A strategy to expeditious invasive treatment improves clinical outcome in comatose patients with aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective In patients with poor clinical condition after aneurysmal subarachnoid hemorrhage (aSAH), treatment is often deferred until patients show signs of improvement. Early external ventricular drainage and aneurysm occlusion may improve prognosis also in poor grade patients. We compared clinical outcome of an expeditious approach to a conservative approach.

Methods 285 consecutive WFNS grade V SAH patients admitted to three university hospitals between January 2000 and June 2007 were included. Two hospitals followed an expeditious approach, one a more conservative approach. Groups were compared with respect to demographic, clinical characteristics and outcome. Univariable and multivariable analyses were performed to determine the associations with good outcome (Glasgow Outcome Scale scores 4-5), using logistic regression models.

Findings Good outcome was seen more often in expeditiously treated patients (22% versus 11%; OR (95% CI): 2.24 (1.17-4.27)). Expeditiously treated patients more often underwent aneurysm occlusion than conservatively treated patients (64% versus 27%; OR (95% CI): 4.86 (2.93-8.05)) and placement of an external ventricular catheter (82% vs 31%; OR (95% CI): 10.05 (5.72-10.66)). There was no significant difference in rebleeding between patient groups. Occlusion of the aneurysm was the only variable that remained significant in the multivariable model with an OR (95% CI) of 43.73 (10.34-184.97).

Interpretation An expeditious invasive treatment strategy in WFNS grade V SAH patients can lead to a better outcome. Hesitance in the early stages seems a self-fulfilling prophecy for a poor outcome.

INTRODUCTION

About a quarter to a third of the patients with an aneurysmal subarachnoid hemorrhage (aSAH) are in a poor clinical condition on admission[1]. This poor clinical condition is associated with poor prognosis[2–4]. Therefore, many centers have adopted a more conservative approach to these patients compared to patients admitted in a good clinical condition, postponing external ventricular catheter (EVC) placement, aneurysm occlusion, or both, until patients show signs of improvement in the first 24-48 hours[3–6]. This watchful-waiting strategy potentially leaves patients at risk of rebleeding and, possibly, increased intracranial pressure. In patients who do not show any improvement in the early stages after admission, delay of invasive treatment may easily lead to defeatism and to do-not-resuscitate orders, which may further make a poor clinical outcome a self-fulfilling prophecy.

Studies have shown that early expeditious aneurysm treatment in poor grade patients can result in a good outcome in up to a third of all cases, but most of these studies also included lower grade patients[5,7]. We reported a favorable clinical outcome in about one fifth of all patients presenting with WFNS grade V aSAH (Glasgow Coma Scale (GCS) between 3 and 6[8]) using an expeditious treatment strategy, which includes early EVC placement and early aneurysm occlusion[9]. As this suggests that refraining from invasive treatment in WFNS grade V SAH patients may no longer be acceptable, we compared the clinical outcome of expeditiously treated WFNS grade V SAH patients to the clinical outcome of patients treated according to the usual, more conservative, strategy.

METHODS

Patient population

Data of 1424 consecutive patients admitted with an aSAH between January 1st 2000 and June 30th 2007 at three university hospitals in the Netherlands (Academic Medical Center (AMC) and VU University Medical Center (VUmc) both in Amsterdam, and the University Medical Center in Utrecht (UMCU)) were collected. All three hospitals act as tertiary referral center for SAH patients. During the study period, both centers in Amsterdam followed the same expeditious treatment strategy (early aneurysm occlusion and placement of an EVC) (group A) whereas the UMCU followed a more conservative treatment strategy (group B). Of all admitted SAH patients, 24% (126/525) in Amsterdam were WFNS grade V and 18% (159/899) in Utrecht.

There was no objection of the Medical Ethics Committee of the AMC to perform this study.

Data Collection

Data were collected retrospectively (group A)[9] or prospectively (group B). Clinical outcome data of the patients from group B was collected by a stroke nurse either in the outpatient clinic or by telephone interview.

Data with respect to demographic characteristics, GCS score on admission, Fisher grade[6], intracerebral hematoma (ICH), ICH diameter, epileptic seizures at presentation, rebleeding, presence of hydrocephalus during the admission period, delayed cerebral ischemia (DCI), interventions (i.e. coiling, surgical clipping and EVC placement), mortality and clinical outcome at three months using the Glasgow Outcome Scale (GOS) was collected[10]. ICH diameter was measured as the maximum diameter in centimetre on plain CT. Hydrocephalus was scored as marked ventricular dilatation on a plain computed tomography (CT)-scan by a neuroradiologist in all participating centers. Epileptic seizures at admission were scored if this was suspected at the ictus or shortly afterwards.

DCI was defined as a new focal neurological deficit (motor or speech) or a decrease of 2 points or more on the GCS, for at least one hour that could not be attributed to other causes such as hydrocephalus, electrolyte or metabolic disturbances, rebleeding or post-treatment complications or infections[11].

Local treatment protocol

Patients in group A were admitted to the intensive care unit and subjected to an expeditious treatment policy, except for those patients who had an absence of all brainstem reflexes (bilateral dilated and fixed pupils, absent corneal reflexes and absent oculocephalic reflexes). A plain CT was performed in all patients on admission. An EVC was placed with a low threshold if raised intracranial pressure was suspected (irrespective of the size of the ventricles) for cerebrospinal fluid (CSF) drainage. A CT-angiography and/or digital subtraction angiography was used to show the presence of an aneurysm, which was either coiled or clipped. The choice of aneurysm treatment was made in consensus by the vascular neurosurgeons and the interventional neuroradiologists. Aneurysms were treated as soon as possible after admission, preferably within 24 hours.

Patients from group B were treated according to the local treatment protocol, which bares close resemblance to the treatment protocol of group A. The main differences were the approach of treatment in patients from group B was less aggressive with respect to placement of an EVC and aneurysm occlusion. An EVC was only placed in case of CT-scan proven hydrocephalus and performing a lumbar puncture was not possible. In the event of no other explanation than the initial insult of the hemorrhage for the comatose condition, such as hydrocephalus, (subclinical) epilepsy or an intracerebral or subdural hematoma, the policy was to wait for 24–48 hours until spontaneous clinical improvement. If patients improved to a Glasgow Motor score of at least 4, aneurysm occlusion, was initiated as soon as logistically possible. If these patients developed hydrocephalus after improvement this was treated accordingly.

Statistical analyses

Continuous variables were tested with the Shapiro-Wilk test for normal distribution (W-statistic > 0.9). If normally distributed, variables were tested with the Student's t-tests, if not the Mann-Whitney U test was used. Categorical variables were tested using the Fisher's exact test.

Clinical outcome in the expeditious and conservative groups was also compared using the Fisher's exact test in three specific subgroups:

1) patients who underwent aneurysm occlusion (irrespective of receiving an EVC)
2) patients who had an EVC without aneurysm occlusion
3) patients who had no treatment (no aneurysm occlusion, nor an EVC)

In the statistical analyses including clinical outcome, the GOS score was used as a dichotomous variable (GOS 4-5: good clinical outcome, GOS 1-3: poor clinical outcome). To determine if there are significant associations between patient characteristics (age, treatment strategy, GCS at admission (GCS 3 or GCS > 3), Fisher grade (Fisher < 4 or Fisher 4), seizures at admission, rebleeding, hydrocephalus, DCI, aneurysm occlusion, EVC) and clinical outcome, univariable analyses were performed using logistic regression models. Variables which were significantly related to good clinical outcome in the univariable analysis were included in a multivariable backward (manually performed) logistic regression model. Values of $p<0.05$ were considered statistically significant.

RESULTS

Patient characteristics

Conservatively treated patients experienced seizures on admission more often than expeditiously treated patients, but this was not significant (OR (95% CI) 0.47 (0.22-1.03)) (table 1). Both placement of an EVC (OR (95% CI) 10.05 (5.72-10.66)), as well as aneurysm occlusion (OR (95% CI) 4.86 (2.93-8.05)) were performed in significantly higher proportions of expeditiously treated patients, although there were no significant differences in hydrocephalus (OR (95% CI) 1.07 (0.59-1.93)), ICH occurrence (OR (95%) 1.06 (0.63-1.80)) or rebleeding (OR (95% CI) 0.95 (0.55-1.65)) between both groups.

Table 1. Baseline and clinical characteristics of 285 patients with a WFNS grade V subarachnoid hemorrhage

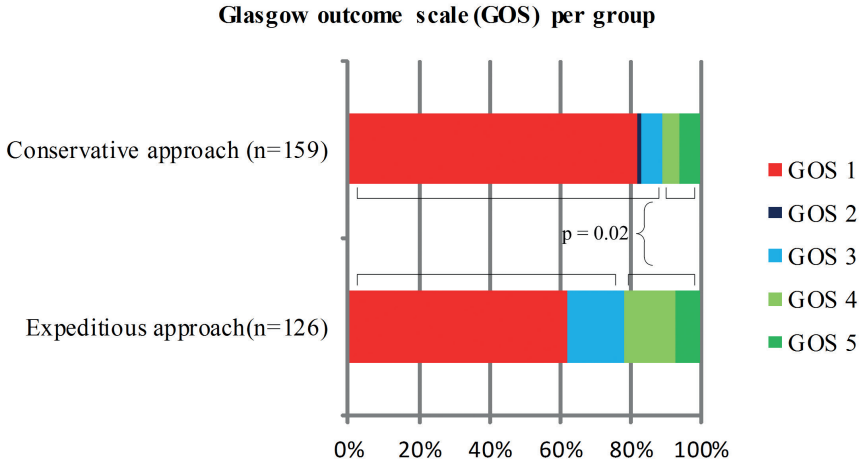
	Total	Expeditious strategy	Conservative strategy	Odds ratio (95% CI)
Patients, n	285	126	159	
Age, mean (SD)	54.60 (14.42)	53.94 (14.18)	55.12 (14.64)	0.99 (0.98-1.01)
Female, n (%)	185 (65)	83 (66)	102 (64)	1.08 (0.66-1.76)
*Fisher grade 4, n (%)**	242 (85)	112 (89)	130 (94)	0.55 (0.23-1.33)
Intracerebral hematoma, n (%)[†]	92 (40)	50 (40)	42 (39)	1.06 (0.63-1.80)
Intracerebral hematoma diameter (cm), mean (SD)[§]	5.02 (2.12)	4.68 (2.06)	5.36 (2.16)	0.86 (0.69-1.06)
Seizures at presentation, n (%)	34 (12)	10 (8)	24 (15)	0.47 (0.22-1.03)
Rebleeding, n (%)	67 (24)	29 (23)	38 (24)	0.95 (0.55-1.65)
Hydrocephalus, n (%)	229 (80)	102 (81)	127 (80)	1.07 (0.59-1.93)
Delayed cerebral ischemia, n (%)	33 (12)	17 (14)	16 (10)	1.39 (0.67-2.88)
External ventricular catheter, n (%)	152 (53)	103 (82)	49 (31)	10.05 (5.72-10.66)
Days after admission external ventricular catheter placement, median (IQR)	0 (0-1)	0 (0-1)	1,00 (0-2)	0,92 (0,84-0,99)
Occlusion of the aneurysm, n (%)	124 (44)	81 (64)	43 (27)	4.86 (2.93-8.05)
Coiling, n (%)	86 (30)	61 (49)	25 (16)	
Clipping, n (%)	38 (13)	20 (16)	18 (11)	

WFNS: World Federation of Neurological Surgeons; SD: standard deviation; IQR: interquartile range. Odds ratio with conservative treatment as the reference category; *n=20 missing in the conservative group. [†]n=2 missing in the expeditious group, n=51 missing in the conservative group. [§]n=10 missing in the expeditious group, n=2 missing in the conservative group.

Clinical outcome comparison between treatment strategies

Three months after the ictus, patients receiving expeditious treatment more often had a good clinical outcome (22% versus 11%; OR (95% CI) 2.24 (1.17-4.27), figure 1)) and died less often (62% versus 82%; OR (95% CI) 0.36 (0.21-0.62), figure 1). Clinical outcome in the expeditious and conservative groups was also compared in specific subgroups. Within all three subgroups there were no significant differences in the proportion of patients with a good (or poor) clinical outcome between the expeditious and the conservative group (figure 2A: patients who underwent aneurysm occlusion (irrespective of receiving an EVC), OR (95% CI) 0.89 (0.41-1.92); figure 2B: patients who had an EVC without aneurysm occlusion, OR (95% CI) 0.96 (0.87-1.05); figure 2C: patients who had no treatment (no aneurysm occlusion, nor an EVC), OR (95% CI) 0.99 (0.97-1.01)).

Figure 1. Glasgow Outcome Scale at three months in 285 patients with a WFNS grade V subarachnoid hemorrhage



p-value is based on the Fisher's exact test analysing the difference between good outcome (GOS 4-5) and poor clinical outcome (GOS 1-3) in the conservatively treated group and expeditiously treated group.

Table 2. Univariable associations with good outcome in 285 patients with a WFNS grade V subarachnoid hemorrhage

Characteristics	N	Odds ratio	95% CI	p*
Group				**0.02**
Expeditious approach	126	**2.24**	**1.17 - 4.27**	
Conservative approach	159	Reference	-	
Age	285	**0.97**	**0.95 - 0.99**	**0.01**
GCS at admission				0.65
GCS 4-6	53	1.25	0.51 - 3.05	
GCS 3	75	Reference	-	
Fisher grade				**0.03**
3 or lower	23	**3.05**	**1.21 - 7.72**	
4	242	Reference	-	
Intracerebral hematoma				0.93
Yes	92	0.97	0.49-1.93	
No	74	Reference	-	
Seizures at presentation				0.20
Yes	34	1.76	0.74 – 4.17	
No	248	Reference	-	
Rebleeding				0.07
Yes	67	0.44	0.18 – 1.08	
No	218	Reference	-	
Hydrocephalus				0.67
Yes	229	1.19	0.52-2.73	
No	45	Reference	-	
Delayed cerebral ischemia				0.07
Yes	33	2.18	0.94-5.10	
No	252	Reference		
External ventricular drainage				**< 0.01**
Yes	152	**4.43**	**2.05 - 9.59**	
No	133	Reference	-	
Occlusion of the aneurysm#				**< 0.01**
Yes	124	**43.73**	**10.34 - 184.97**	
No	161	Reference	-	

GCS: Glasgow Coma Scale. *tested with binary logistic regression. #Occlusion of the aneurysm includes surgical clipping and coiling procedures.

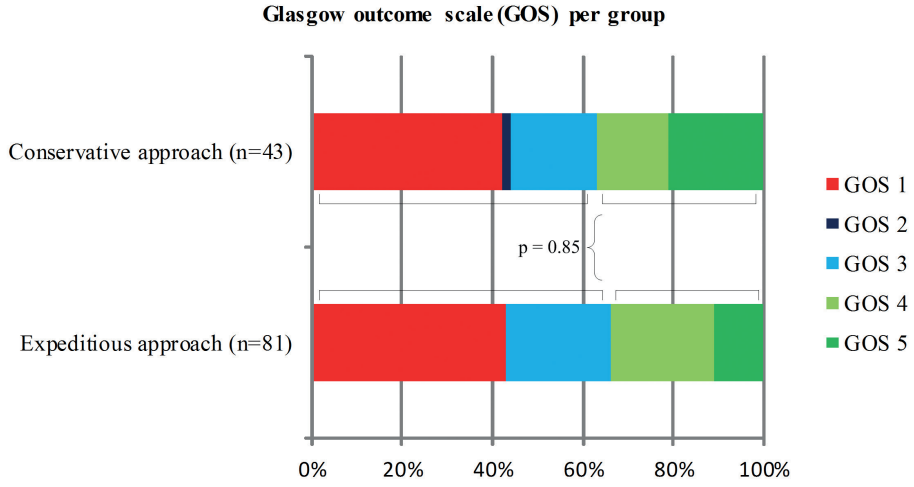
Associations with good clinical outcome

Univariable analyses revealed significant associations between good clinical outcome and expeditious treatment strategy, younger age, Fisher grade <4, EVC, and aneurysm occlusion, with the strongest associations for aneurysm occlusion (OR (95% CI): 43.73

(10.34-184.97)) and EVC placement (OR (95% CI): 4.43 (2.05-9.59)) (table 2). The multivariable analysis showed that aneurysm occlusion was the only variable that remained in the multivariable model with an OR (95% CI) of 43.73 (10.34-184.97). Due to the relatively large difference in seizures at admission between group A and B, the analysis was also performed including taking the potential influence of seizures into account, which did not change the results. The association between good clinical outcome and aneurysm occlusion is visualised in supplemental figure 3.

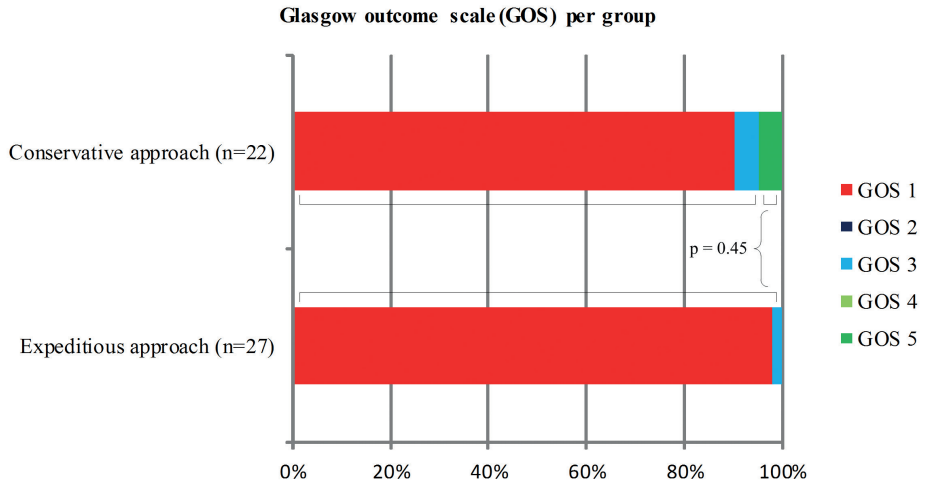
Figure 2. Subgroup analyses

Figure 2A. Groups based on treatment approach and aneurysm occlusion (irrespective of receiving an EVC)



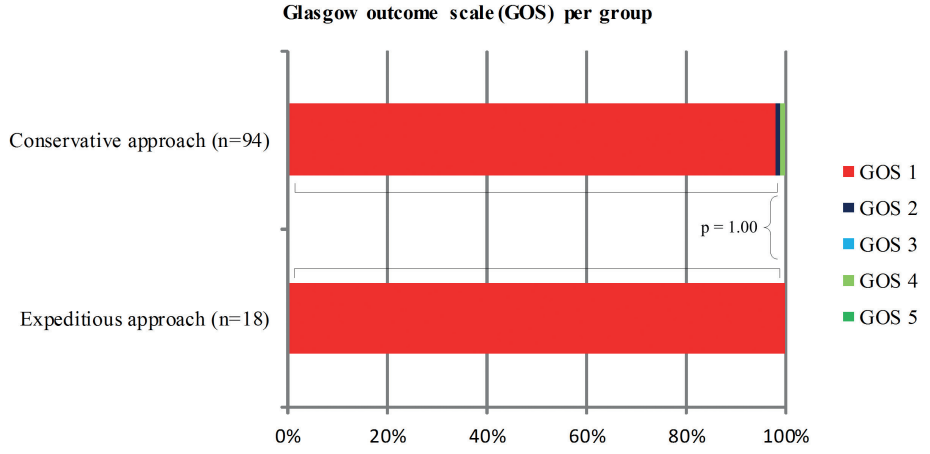
p-value is based on the Fisher's exact test analysing the difference between good outcome (GOS 4-5) and poor clinical outcome (GOS 1-3) in patients within the conservatively treated group and expeditiously treated group in which the aneurysm was occluded (irrespective of receiving an EVC).

Figure 2B. Groups based on treatment approach and EVC placement (without aneurysm occlusion)



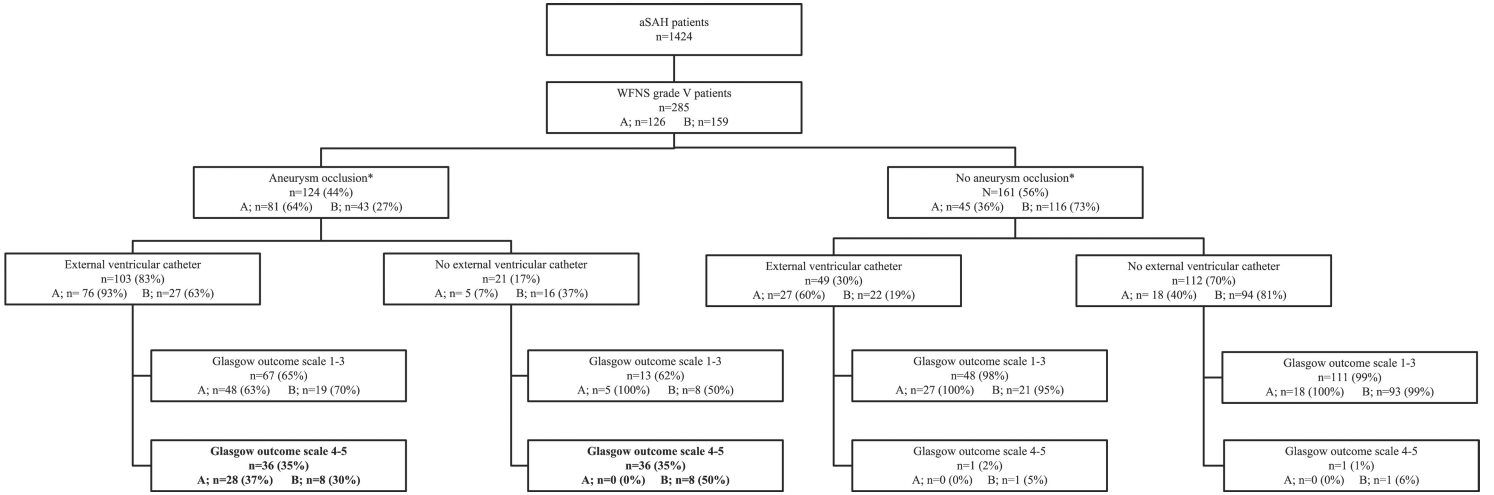
p-value is based on the Fisher's exact test analysing the difference between good outcome (GOS 4-5) and poor clinical outcome (GOS 1-3) in patients within the conservatively treated group and expeditiously treated group in which an EVC was placed (without aneurysm occlusion).

Figure 2C. Groups based on treatment approach and no treatment (no aneurysm occlusion, nor an EVC)



p-value is based on the Fisher's exact test analysing the difference between good outcome (GOS 4-5) and poor clinical outcome (GOS 1-3) in patients within the conservatively treated group and expeditiously treated group in which no intervention was performed (no aneurysm occlusion, nor an EVC).

Figure 3. Flow chart regarding aneurysm occlusion and external ventricular drainage in all 285 patients with a WFNS grade V subarachnoid hemorrhage



SAH Subarachnoid hemorrhage. *WFNS* World Federation of Neurological surgeons. *Aneurysm occlusion includes surgical clipping and coiling procedures.

DISCUSSION

Because patients with a grade V aSAH generally have a very poor prognosis, many physicians start invasive treatment only if patients show signs of improvement, fearing that interventions in patients in a poor condition will lead to more patients surviving in a vegetative or minimally conscious state. We found that good outcome was achieved in a significantly higher proportion of the expeditiously treated patients. Aneurysm occlusion was the only variable that remained in the multivariable model determining significant associations with good outcome.

Hydrocephalus was almost similar in both treatment groups. However, in the expeditiously treated group an EVC was placed significantly more often as EVC placement is a mainstay of the expeditious approach, and catheters were sometimes placed in patients without ventricular enlargement to just reduce intracranial pressure. It may also indicate hesitance to the EVC placement in poor condition patients in the conservative group. Possibly withholding patients the opportunity to improve to a level of consciousness when aneurysm treatment would be initiated.

Aneurysm treatment after aSAH (coiling or clipping) is aimed to prevent rebleeding. Three-quarters of episodes of rebleeding occur in the first three days after aSAH and is associated with poor prognosis[12,13]. Since rebleeding mostly occurs on the first day after aSAH, there is strong evidence for early aneurysm treatment[5,7,13–15]. Nevertheless, although aneurysm treatment was strongly associated with good outcome, the analyses indicate that this strong positive effect of aneurysm treatment on outcome cannot be explained by prevention of rebleeding, since there were no significant differences in rebleeding between treatment groups. The occurrence of rebleeding may have been somewhat underestimated as these patients are in a very poor clinical condition, either being comatose or sedated, making it more difficult to show further deterioration and rebleeding can occur subclinical. This underestimation would however be the same for both groups.

As patients in the conservative strategy group were only treated by coiling or clipping after they had progressed to a better neurological condition, one would expect that the outcome of the group coiled and clipped patients in the conservative group would be better than the outcome of the group coiled and clipped patients in the expeditiously treated patients, as the latter group contained many more patients in a worse clinical condition. Surprisingly, no significant differences in

good (or poor) clinical outcome between these groups were found (figure 2A). In other words, the mere initiation of invasive treatment leads to a higher survival rate and better outcome at three months. Not surprisingly, comparison of all patients without aneurysm occlusion but with an EVC or patients without any intervention (figures 2B and 2C), showed a universally dismal clinical outcome in both the conservatively and expeditiously treated groups.

Studies in patients with an intracerebral hemorrhage have shown that early withdrawal of life support or do-not-resuscitate orders lead to death and thus serve as a self-fulfilling prophecy and a poor clinical outcome overall[16]. Expeditious treatment was only different in a higher tendency to start coiling/clipping or EVC placement resulting in the observed higher treatment rate. The statistical model in this study reveals that aneurysm occlusion is strongly associated with good outcome in WFNS V aSAH patients. As the positive effect on clinical outcome at three months of an expeditious approach found in our study cannot be explained by the prevention of rebleeding, it is therefore most likely attributable to a different mind-set. Once (multidisciplinary) treatment has been initiated, physicians will be less likely to stop treatment, as it has been shown that when patients have been operated on, life support is infrequently discontinued[16,17], and continuing treatment gives patients more time to improve clinically. More aggressive treatment provides more workload for the treating physicians, also leads to more experience, which is proven to result in better outcome[18]. Hesitance in treatment on the other hand, or no treatment whatsoever of patients in a poor condition, leads to a worse clinical outcome and more frequently to the demise of these patients. Beyond this mind-set and the difference in treatment initiation (aneurysm treatment and/or EVC) there are possibly more subtle differences, which are difficult to measure between different hospitals, although the general treatment was comparable.

This study has limitations. A first limitation is the relatively small sample size, leading to less precise estimates. A second limitation is the scoring of hydrocephalus, which was score by a neuroradiologist, not based on objective criteria, which leaves room for misinterpretation. A third limitation is the partly retrospective nature of this study, in which. The outcome scores in the expeditious group were retrieved from information from the patient charts. Whereas in the conservative group this was done by independent observers, possibly causing an underreporting of poor outcome in the expeditious group. This will of course not have influenced the case fatality rates. With these limitations in mind the point estimates of the odds ratios

have a certain level of uncertainty, nevertheless the direction of our results will not have been influenced by the limitations. Further research into these patients is needed to support our conclusions. To summarise patients in the expeditious group reached better outcome. Comparison of actually treated patients between units did not show a different outcome. Despite the fact that rebleeding did not occur less, aneurysm treatment seems to be the most significant association with good outcome. We hypothesise that a different mind-set towards treatment is in large part responsible for the improved outcome in the expeditious treated group.

CONCLUSION

An expeditious invasive treatment strategy in WFNS grade V SAH patients can possibly lead to a better outcome, irrespective of rebleeding prevention, and can be considered. Hesitance based on doubt about realistic chances of meaningful recovery in the early stages after aSAH in these patients can be a self-fulfilling prophecy for a poor outcome.

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CHAPTER 6:

Early treatment decisions in poor-grade patients with a subarachnoid hemorrhage

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ABSTRACT

Background Patients with WFNS grade V subarachnoid hemorrhage (SAH) mostly have a poor outcome. Correct identification of patients, who might benefit from treatment, remains challenging. We investigated which disease-related characteristics, present at admission, could identify patients with chance of good outcome.

Methods 146 consecutive WFNS grade V SAH patients (2002 – 2013) were included. Demographic and disease-related characteristics were compared between patients with a good outcome (Glasgow outcome scale (GOS) 4 & 5) and a poor outcome (GOS 1-3). Subgroups were made of patients with aneurysm treatment according to outcome; 1) good outcome, 2) poor outcome, with optimal general treatment, 3) poor outcome, general treatment discontinued.

Results 34 of the 146 patients had a good outcome (36% of all treated patients); 16 (47%) of these presented with a GCS score of 3, versus 65 (58%) of patients with a poor outcome ($p = 0.33$). Eleven (33%) patients in the good outcome group presented with pupillary abnormalities; four (12%) even had bilaterally fixed and dilated pupils, versus 49 (46%) in patients with a poor outcome ($p < 0.01$). In 51 patients the aneurysm was not treated; all died.

Conclusions Over a third of all treated WFNS grade V SAH patients had a good outcome. All patients, in whom the aneurysm was not treated, died. Reliable identification of patients who will reach good outcome, on the basis of symptoms on admission, seems impossible, as these symptoms are not discriminating enough.

INTRODUCTION

The clinical outcome of patients who present with a World Federation Neurosurgical Society (WFNS) grade V subarachnoid hemorrhage (SAH) is often poor, and the mortality rate, despite treatment, is high[1–3]. The reasons for the demise of these patients vary widely. Some die in the acute phase because of cerebral herniation caused by massive intraparenchymal hemorrhage, diffuse cerebral edema and ischemia, or hemodynamic instability[2,3]. Others are threatened in the subacute phase by complications of aneurysm treatment, and other medical complications, such as delayed cerebral ischemia or infections, which may all lead to poor outcome or death[3]. If patients survive the initial phase, treatment is sometimes discontinued when recovery to meaningful daily living is no longer deemed realistic. This includes discontinuation of respiratory support, limitation of further treatment of new medical problems such as infections, respiratory or cardiac failure, or a combination of these. Since these patients are already in a poor clinical condition on admission, they are traditionally approached in a conservative manner, withholding treatment of the causative aneurysm or placement of external ventricular catheter, until they show signs of neurological improvement[4]. We have previously shown that a more expeditious strategy towards aneurysm treatment in WFNS grade V patients is associated with a more favorable outcome, sometimes with minor deficits, in as much as 22-39%[5,6]. Hesitancy in treatment leads to a self-fulfilling prophecy for a poor clinical outcome[6]. It has been shown that neurological scoring according to the WFNS grade may not represent the best predictor for a good or poor outcome[7]. Grading after resuscitation with placement of an external ventricular catheter (EVC), decompressive craniotomy or space occupying hematoma is proven to be a better predictor for outcome. This however, does not help to discriminate the patients at admission and the question remains, how to select, before initiation of treatment, those patients for expeditious treatment who have the highest chance for a good outcome, as well as how to select those patients for whom treatment would be futile. Therefore, we compared the demographic and disease-related characteristics on admission of WFNS grade V SAH patients, in order to gain more insight into the current selection process for treatment of poor-grade SAH patients.

MATERIAL AND METHODS

Patient population

The Academic Medical Center (AMC) acts as a tertiary referral center for patients with an aneurysmal SAH in the Amsterdam Metropolitan Area with a total population of approximately 2.5 million people. During the period from January 1st, 2002 to July 1st, 2013, 164 patients were admitted with a WFNS grade V SAH. Fourteen patients with ruptured aneurysms, which were deemed to be 'not treatable' by coiling or clipping, solely based on aneurysm characteristics, were excluded, as, in these patients, the decision not-to-treat was not based on their clinical condition. Four patients were lost to follow-up; the remaining 146 patients were included in the present study.

There was no objection of the Medical Ethics Committee of the AMC to perform this study.

Data collection

Clinical records were examined retrospectively. Data with respect to demographic characteristics, Glasgow Coma Scale (GCS) and WFNS score on admission, pupillary reflexes, brainstem reflexes, epileptic seizures at presentation, rebleeding, the presence of hydrocephalus, location of aneurysm, type of interventions (i.e. coiling, surgical clipping and placement of an EVC, and case fatality were collected. Neurological assessment was performed as soon as possible after admission in the treatment center (AMC). If a patient was sedated and intubated before arrival in the treatment center, the last known neurological examination before sedation was used. The WFNS grade is a five-point (I-V) neurological grading scale based upon the Glasgow Coma Scale (GCS), in which a higher score indicates a worse clinical condition. A WFNS grade V represents a GCS score between 3 and 6[8]. The WFNS grade was determined as early as possible, before resuscitation (including placement of an external ventricular catheter (EVC)). Rebleeding was defined as a new bleeding from the causative aneurysm after the initial bleeding. This was determined as an increase of blood on a plain CT-scan of the head, or when a patient experienced an outflow of fresh blood from their EVC. If there was a sudden increase in blood pressure and/or a decrease in consciousness, not otherwise explained, a rebleeding was suspected. The clinical outcome at three months was determined using the Glasgow Outcome Scale (GOS). The GOS is a clinical outcome scale ranging from 1 (death) to 5 (good recovery)[9]. A favorable outcome was defined

as a GOS score of 4 (moderate disability) and 5. For all patients who died during the admission period the reason of demise was collected. If general treatment was discontinued, the reason for discontinuation was extracted from the clinical charts.

Treatment protocol

All patients were treated according to a standardized treatment protocol. A plain computed tomography (CT) was performed on admission, the presence of hydrocephalus was determined by an experienced neuroradiologist. In case of hydrocephalus, or if raised intracranial pressure was suspected (irrespective of the size of the ventricles), an EVC was placed for cerebrospinal fluid (CSF) drainage. Based on CT-angiography and/or digital subtraction angiography, the aneurysm was either coiled or clipped in consensus by the vascular neurosurgeons and the interventional neuroradiologists. Eligibility for aneurysm occlusion was at the discretion of the treating neurosurgeon/interventional neuroradiologist. The aim was to treat the aneurysm as soon as possible, within 24 hours from 2006 onwards.

Statistical analyses

Patients' demographics and disease-related characteristics were compared between patients with a good outcome and patients with a poor outcome. In addition, subgroups were made, according to clinical outcome:

1) Patients with a good outcome;
2) Patients with a poor outcome, with otherwise optimal general treatment,
3) Patients with a poor outcome, in whom general treatment was discontinued after aneurysm treatment.

The obtained data were analyzed using Statistical Package for the Social Sciences Software (IBM SPSS 21.0). Categorical variables were tested using a χ^2 or Fisher's exact test. Continuous variables were tested with the Kolmogorov-Smirnov test for normal distribution. Normally distributed continuous variables are represented as a mean with a standard deviation (SD). Continuous variables that are not normally distributed are represented as a median with an interquartile range (IQR 25%-75%). Normally distributed variables were tested with the Student's t-test (two group comparison) or a one-way ANOVA with Bonferroni post-hoc analysis (multiple group comparison). Data that were not normally distributed were tested with the Mann-Whitney U test (two group comparison) or Kruskall-Wallis test (multiple group comparison). Values of $p < 0.05$ were considered statistically significant.

RESULTS

The baseline characteristics of all 146 patients are presented in table 1. Thirty-four (23%) patients reached a good outcome, whereas 88 (60%) patients died. Of the 95 treated patients, 37 (39%) died. Of all 88 deceased patients, 80 died after treatment limitations were initiated and general treatment was discontinued. Of the patients with a poor outcome, 30 received optimal treatment and in 31 the treatment was discontinued during the clinical course (table 2). There was no difference in age between treated patients with a good or poor outcome.

Patients who had no aneurysm treatment

All 51 patients, in whom the decision was made to refrain from aneurysm treatment, died (median of one day; IQR 1-20)(table 2)(figure 1). These patients were significantly older, presented significantly more often with a GCS score of 3 and two fixed and dilated pupils, than patients with a good outcome and patients with a poor outcome in whom treatment was continued. The reason for not treating the aneurysm was poor neurological condition alone in 22 patients, and a combination of poor neurological condition and complications, or co-morbidities, in 29: neurological condition after cardiopulmonary resuscitation, advanced age, medical complications (e.g. pneumonia, sepsis), or carcinoma. In all 12 patients with a rebleed, this event occurred before the decision was made not to treat the aneurysm.

Patients who had aneurysm treatment with a good outcome

A good outcome was reached in 34 (23% overall, 36% of all treated patients) patients (table 1&2). Of these, 16 (47%) presented with a GCS score of 3, whilst 65 (58%) patients with a poor outcome presented with a GCS score of 3 ($p = 0.33$). Eleven (33%) patients presented with pupillary abnormalities. Four (12%) patients even had bilaterally fixed and dilated pupils, compared to 49 (46%) patients with a poor outcome ($p < 0.01$)(table 1), i.e. significantly less than untreated patients and patients with a poor outcome in whom treatment was discontinued (35 (71%) and 9 (31%) respectively)(table 2). All patients who had a good outcome underwent aneurysm treatment, whereas almost half of the patients with a poor outcome did not undergo aneurysm treatment ($p < 0.01$)(table 1).

Table 1. Characteristics of all 146 patients with a WFNS V subarachnoid hemorrhage and for groups according to outcome

Characteristics	Total, n=146	Poor outcome (GOS 1-3), n=112	Good outcome (GOS 4-5), n=34	P
Age, mean (SD)	54.2 (11.7)	55.0 (12.0)	51.4 (10.3)	0.14
Female, n (%)	91 (62)	66 (59)	25 (74)	0.16
GCS score 3, n (%)	81 (56)	65 (58)	16 (47)	0.33
Pupils[*]				<0.01
Normal, n (%)	63 (45)	40 (38)	23 (68)	
1 fixed and dilated, n (%)	13 (9)	8 (8)	5 (15)	
2 fixed and dilated, n (%)	53 (38)	49 (46)	4 (12)	
2 fixed, n (%)	11 (8)	9 (9)	2 (6)	
Rebleeding, n (%)	23 (16)	20 (18)	3 (9)	0.29
Hydrocephalus, n (%)	76 (52)	58 (52)	18 (53)	0.55
CSF drainage, n (%)	89 (61)	66 (59)	23 (68)	0.43
Seizures at admission, n (%)	7 (5)	5 (5)	2 (6)	0.67
Delayed cerebral ischemia, n (%)	20 (14)	14 (13)	6 (18)	0.57
Treatment				< 0.01
None, n (%)	51 (35)	51 (46)	0 (0)	
Coiling, n (%)	76 (52)	50 (45)	26 (77)	
Clipping, n (%)	19 (13)	11 (10)	8 (23)	
Aneurysm location:				0.11
Anterior circulation, n (%)	83 (57)	61 (55)	22 (65)	
Posterior circulation, n (%)	50 (34)	38 (34)	12 (35)	
Unknown, n (%)	13 (9)	13 (11)	0 (0)	
Glasgow Outcome Scale				
1 – 3, n (%)	112 (77)			
4 -5, n (%)	34 (23)			

WFNS World Federation of Neurosurgical Societies, *GCS* Glasgow Coma Scale, *CSF* Cerebral Spinal Fluid, Good outcome is defined as a Glasgow Outcome Scale of 4 and 5, a poor outcome as 1 till 3
[*]6 missing poor outcome group.

Patients who had aneurysm treatment, with a poor outcome with otherwise optimal general treatment

Thirty patients (20%) received optimal treatment, but had a poor outcome at follow-up. There were no differences in baseline characteristics compared with both

other treated aneurysm groups (table 2). Six patients died a median 49 days after admission (IQR 25.5-82.5) (table 2). Four patients were transferred to care homes where the treatment was discontinued in the later stages due to the absence of further improvement.

Table 2. Characteristics of 146 patients with a WFNS V subarachnoid hemorrhage according to aneurysm treatment and outcome

Characteristics	**Untreated aneurysm**	**Treated aneurysm good outcome**	**Treated aneurysm, poor outcome**	
	n=51	n=34	**treatment continued, n=30**	**treatment discontinued, n=31**
Age, mean (SD)	57.0 (12.5)[a,b]	51.3 (10.3)	53.3 (10.1)	53.1 (12.7)
Female, n (%)	23 (45)[a,b]	25 (74)	22 (73)	21 (68)
GCS score 3, n (%)	33 (65)[b]	16 (47)	12 (40)	20 (65)
Pupils[*]				
Normal, n (%)	10 (20) [a,b,c]	23 (67) [d]	16 (58)	14 (49)
1 fixed and dilated, n (%),	2 (4)	5 (15)	3 (11)	3 (10)
2 fixed and dilated, n (%)	35 (71)	4 (12)	5 (18)	9 (31)
2 fixed, n (%)	2 (4)	2 (6)	4 (13)	3 (10)
Rebleeding, n (%)	12 (24)	3 (9)	2 (7)	6 (19)
CSF drainage, n (%)	25 (49)	23 (68)	21 (70)	20 (65)
Seizures at admission, n (%)	3 (6)	2 (6)	1 (3)	1 (3)
Days till aneurysm treatment, mean (SD)	-	1.2 (3.1)	0.8 (1.0)	0.6 (0.8)
Deceased, n (%)	51 (100)[a,b,c]	0 (0)[d,e]	6 (20)[f]	31 (100)
Days till death, median (IQR)	1.0 (1.0-2.0)[b,c]	-	49.0 (25.5-82.5)[f]	12.0 (4.0-24.0)

WFNS World Federation of Neurosurgical Societies, *GCS* Glasgow Coma Scale, *CSF* Cerebral Spinal Fluid, Good outcome is defined as a Glasgow Outcome Scale of 4 and 5.

[a]$p \leq 0.05$ between untreated aneurysm and treated aneurysm good outcome

[b]$p \leq 0.05$ between untreated aneurysm and treated aneurysm poor outcome treatment continued

[c]$p \leq 0.05$ between untreated aneurysm and treated aneurysm poor outcome treatment discontinued

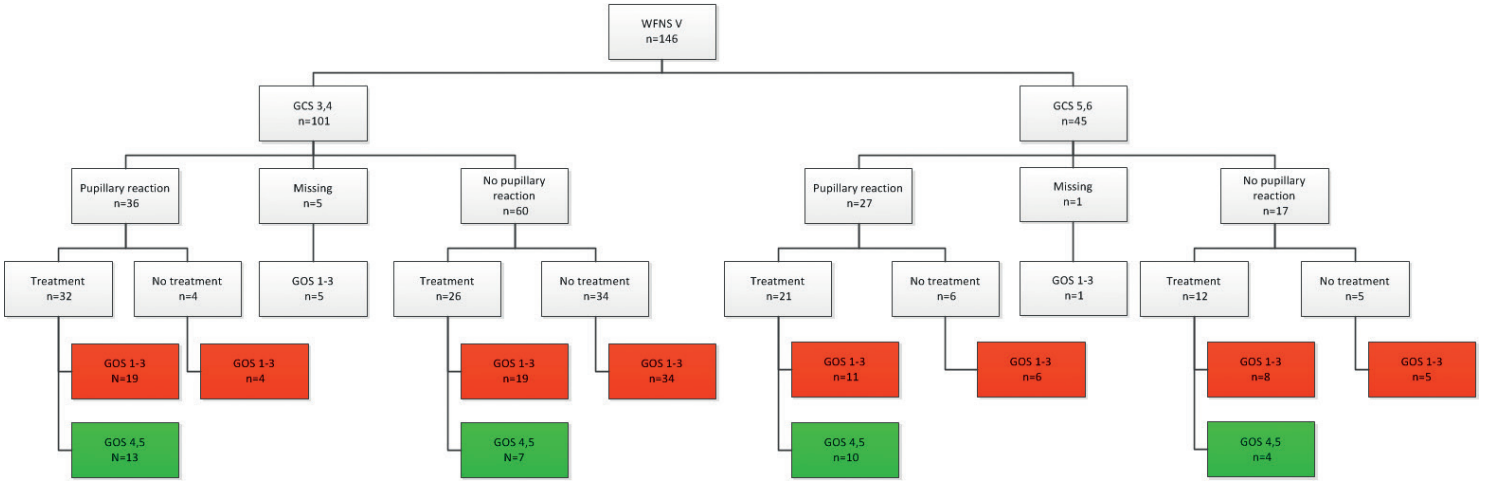
[d]$p \leq 0.05$ between treated aneurysm good outcome and treated aneurysm poor outcome treatment discontinued

[e]$p \leq 0.05$ between treated aneurysm good outcome and treated aneurysm poor outcome treatment continued

[f]$p \leq 0.05$ between treated aneurysm poor outcome treatment continued and treatment discontinued

[*]2 missing in untreated group, 2 missing in treated aneurysm poor outcome continued en 2 missing in discontinued

Figure 1: Flow chart regarding clinical outcome of 146 WFNS grade V subarachnoid hemorrhage patients according to treatment.



WFNS World Federation of Neurological surgeons. *GCS* Glasgow Coma Scale. *GOS* Glasgow Outcome Scale

Patients who had aneurysm treatment, with a poor outcome, in whom general treatment was discontinued after aneurysm treatment

In 31 patients, initially treated for their aneurysm, the decision was made during the course of their illness, to discontinue treatment because of a poor prognosis for neurological recovery. All 31 patients died after a median of 12 days (IQR 4.0-24.0) (table 2). The time till aneurysm treatment was not significantly longer for these patients compared to both other treated groups.

Treatment paradigm according to clinical situation on admission

Figure 1 shows the clinical outcome of patients according to treatment, and further subdivision according to GCS and pupillary reaction. All patients who did not undergo aneurysm treatment reached a poor outcome. Of the 26 treated patients with a GCS of 3 and 4 with no pupillary reaction, seven (27%) patients still reached a favorable outcome (figure 1).

DISCUSSION

We compared demographic and disease-related characteristics of treated and untreated WFNS grade V SAH patients in order to gain more insight into the current selection process for treatment of poor-grade SAH patients. A good outcome was reached in 36% of all treated patients, although almost half of the good-outcome patients presented initially with a GCS score of 3, and one third even with one, or two, fixed and dilated pupils. Other studies found that abnormalities in the pupillary response is a prognostic factor for poor outcome[10–12]. Even though we see more than three quarters of our patients with pupillary abnormality in our population reach a poor outcome they also constitute a third of the good outcome group. Due to the high population density in the Netherlands, and especially in the Amsterdam Metropolitan Area, and the relatively short travel distances, patients tend to be presented rapidly to a referral center after their SAH. As their neurological condition may still be dominated by the event of the initial ictus, seizures or acute hydrocephalus[13], the neurological examination could be biased towards a worse neurological status on admission, and this might explain why initial neurological condition does not discriminate well for a good clinical outcome. On the other hand, because of a poor initial neurological condition, we may not have treated some patients who might have reached a good outcome if we had initiated treatment. All patients, in whom the decision was made not to treat the aneurysm, died soon after admission. It is difficult to predict whether there

are patients in this group who might have reached a good outcome if treatment had been initiated. At baseline, there were no significant differences with the patients in whom the treatment was continued and the patients who did have a good outcome. Several prognostic models have tried to select which patients would benefit from aggressive treatment, but the problem with these models is that they are based on treatment decisions, which have already been made[14–16]. It has been shown that assessment of the neurological status after placement of an EVC to correct an acute hydrocephalus and/or raised intracranial pressure, removal of a space occupying hematoma and/or decompressive craniotomy will lead to a more reliable prediction of the outcome[5,7,17]. This however would mean that all patients would need to receive an EVC and/or undergo a craniotomy and wait for neurological improvement, even in the extremely poor cases, which is not common practice in most neurosurgical centers. The decision to proceed towards these first steps of resuscitation and treatment is made in many cases by the neurosurgeon or the neuroradiologist on call. Without a clear algorithm defining which patients to treat, and which not, there will be discongruity amongst physicians which patients they deem too poor for aneurysm treatment. This might well explain our observation that one or two fixed and dilated pupils was a reason not to proceed towards treatment in one patient, but to initiate urgent treatment in another. There is a good clinical outcome in more than 10% of patients, who were treated despite bilaterally fixed and dilated pupils. Thus, the initial neurological score at admission, including pupillary reaction, before resuscitation alone may not be reliable to predict the outcome in WFNS grade V patients.

In all patients with a rebleed, this event occurred before the decision was made not to treat the aneurysm. Even earlier securing of the aneurysm might have prevented rebleeds in these patients. Although a previous prospective study suggested that there is no added effect of early treatment in SAH patients in a poor clinical condition[18], other (and more recent) studies have shown that treatment within 24 hours by coiling improves the outcome in Hunt-Hess grade IV and V SAH patients[19,20].

A limitation of this study is the relative short follow-up period. Though it leads to the least patients lost to follow-up, it might under- or even overestimate the outcome results. Another limitation of this retrospective study is that we reviewed decisions 'in hindsight'. Decisions which were made in a seriously ill group of patients, under the daily pressure of having to allocate limited time and resources, preferably to those patients who have the best chance of survival and a meaningful recovery.

It is therefore, not possible to judge in retrospect whether the decisions that were made were justified, more so, as they are also influenced by factors personal to the physician (experience, culture, religion etc.)[21]. It is clear however, that decisions, based purely on baseline characteristics, and made early after admission to the hospital, might not be in the best interest of all patients, even of those patients who present in a deplorable neurological condition, and in whom treatment is seemingly futile. Far more accurate knowledge of which patients would benefit from expeditious treatment is needed. In an ideal situation, a prospective clinical trial in which inter-physician variability is eliminated could help answer this question, although a randomized controlled trial might be unethical in these patients. In the meanwhile, we think that this study supports the expeditious treatment of WFNS grade V patients, even in those with a poor condition on admission.

CONCLUSIONS

Reliable identification, on the basis of clinical symptoms on admission, of WFNS grade V SAH patients who will have a good outcome seems impossible. The neurological examination at admission alone should not serve as a basis for the decision to proceed towards or withholding treatment, as even the most severe cases have a chance of recovery.

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CHAPTER 7:

General discussion and future directions

GENERAL DISCUSSION

Patients who present in a poor clinical and neurological condition after a subarachnoid hemorrhage (SAH) usually have a poor clinical outcome[1,2]. Besides the initial condition due to the ictus, patients with an SAH are under threat from secondary deterioration. This can initially be caused by seizures, acute hydrocephalus, cardiac or respiratory complications, or rebleeding[3]. In later stages patients may experience deterioration caused by complications such as delayed cerebral ischemia (DCI) and infections, e.g. shunt-related ventriculitis and delayed hydrocephalus[3,4]. The initial poor condition as well as the secondary threats contribute to a poor clinical outcome. Therefore, despite advances in treatment in recent years, such as endovascular treatment and improved supportive care in the ICU, SAH remains a devastating disease with a high morbidity and mortality affecting patients of all ages, but mostly in their middle-age[3,5]. Patients who present in a very poor clinical condition (WFNS grade 4 or 5) are mostly treated in a conservative manner to see whether the neurological condition improves spontaneously, but this has a direct influence on their clinical outcome.

In the first part of this thesis we investigated the factors associated with complications resulting in a poor outcome. In particular the time intervals between subarachnoid hemorrhage and aneurysm treatment to determine whether there is a delay in treatment that leaves patients susceptible to rebleeding. Secondly, we explored the challenges in diagnosing ventriculitis after an SAH. In the second part of this thesis we explored the treatment decisions made in poor-grade SAH patients and the reasons of demise in these patients.

Time intervals after subarachnoid hemorrhage

In most of the literature aneurysm treatment within 24 hours after an SAH is regarded as ultra-early. Early treatment within 72 hours is generally accepted round the world to prevent rebleeds and advocated in guidelines, but there is still no consensus whether ultra-early treatment prevents rebleeding and thus improves outcome[6–13]. Ultra-early treatment, on the other hand, might lead to more periprocedural ruptures in some patients, due to clot instability, offsetting the advantage of ultra-early aneurysm obliteration in others[14].

The majority of the rebleeds occurs within 24 hours, with the median time from ictus to rebleed being between 2 and 3 hours[15,16]. To prevent rebleeding the focus needs to be on the time period before a patient reaches a treatment facility, as well as on the in

hospital period before aneurysm treatment is initiated. In **chapter 2** we explored the intervals between the ictus, admission to a referral hospital, admission to a treatment center and the initiation of aneurysm treatment in a consecutive group of 278 SAH patients[17]. An independent factor contributing to delay was admission in the treatment facility later in the day. In these cases treatment is often postponed till the next day as in most hospitals it is not standard practice to perform aneurysm treatment during out-of-office hours unless it is life-threatening. Would this change if vascular neurosurgeons and interventional neuroradiologists work in shifts? A 24-hour in-house availability of a full treatment team, including an anesthesiology team, would lower the threshold to initiate treatment as soon as possible after admission, even in non-life-threatening situations. However, early endovascular treatment is also seen to be associated with a higher percentage of intra-procedural aneurysm rupture and hematoma growth[14,18,19].

Another independent factor contributing to the delay in treatment is admission to a referral hospital [17]. When one looks where and when rebleeds occur, it has been shown that 13-61% occur before a patient reaches the treatment facility[15,16,20]. It has also been shown that a longer distance and transport time to a treatment facility leads to a worse outcome and is associated with a higher rebleed rate[21,22]. This all emphasizes the need for early transportation directly to a treatment facility, when possible bypassing the referral hospital in the first place. However, if every patient with a headache and/or a decreased consciousness is presented at a treatment facility this would lead to insurmountable logistics. Triage and pre-hospital diagnosis starts from the moment an ambulance is called; for a first responder it will be difficult, especially in an unconscious patient, to differentiate whether a patient has experienced an SAH or an ischemic stroke, or a completely different disease. Additional education of the first responders in recognizing an SAH will still not suffice completely. In rural areas of Norway a mobile stroke unit (MSU) is used to better triage the patients before transferring them to a hospital. A CT-scan is made on the spot, and when an SAH is diagnosed the patient is transferred directly to a treatment center, saving between 120 and 150 minutes in time between ictus and aneurysm treatment[23]. This sounds ideal, especially in countries with large distances between treatment centers, but could probably be less cost-effective in densely populated areas (like The Netherlands).

Ischemic stroke is a much more prevalent disease than SAH and in recent years intra-arterial treatment (IAT) has been a massive success with improvement of the outcome in stroke patients. However, for an IAT to be a success a stroke patient needs to be in a treatment center as soon as possible ("time is brain")[24,25]. As most neurovascular

treatment facilities treat both stroke and SAH patients it would be wise to have the SAH 'ride the wave' of IAT and benefit from the logistical conditions that have been put in to place for IAT; such as 24-hour staffing of interventional neuroradiologists, radiology technicians and anesthesiology teams. This 24-hour service will help to overcome the barrier to treat SAH during the nightly hours and thus pull the 19-hour peak we found between ictus and aneurysm treatment closer to the 4-hour peak. Hopefully, the faster admission in a treatment center will in the future bring the treatment of an SAH patient even within 2-3 hours after the ictus when the highest peak of rebleeding happens.

However, if more evidence becomes available that ultra-early aneurysm treatment is associated with more periprocedural complications, it would still be very important to get a patient to a treatment facility as soon as possible, as there are more options to prevent rebleeding within 24 hours besides aneurysm treatment, such as blood pressure control and early antifibrinolytic therapy. Several trials have investigated the role of antifibrinolytic therapy[26,27]. A Cochrane review showed a 35% reduction in rebleed rate, but did not show an effect on case-fatality or on improving overall outcome. This was probably due to an increase in cerebral ischemia in these trials[26]. As most trials gave antifibrinolytic therapy for a longer period, a multicenter, randomized, open-label trial (ULTRA) with short-term and ultra-early administration of tranexamic acid (TXA) in 950 patients was recently completed, and the results are being awaited[27]. This trial will hopefully provide an answer whether antifibrinolytic treatment not only prevents rebleeds in SAH patients in the first hours after the initial bleeding, but also whether this improves clinical outcome at six months follow-up.

External ventricular drainage-associated ventriculitis after subarachnoid hemorrhage
Nosocomial infections have been shown to affect the clinical outcome in SAH in a negative way[28,29]. A significant portion of SAH patients needs some form of cerebral spinal fluid (CSF) diversion therapy, leaving them at risk of a bacterial ventriculitis. As the symptoms of an SAH closely resemble those of a ventriculitis (like fever, nuchal rigidity and decreased consciousness) the diagnosis of such an infection poses a challenge in daily practice. The influx of red blood cells due to the SAH causes a sterile inflammatory response and cause symptoms resembling those of a bacterial ventriculitis[30,31]. In **chapter 3** we examined which clinical or (routine) laboratory characteristics could help with the diagnosis of a bacterial ventriculitis after an SAH[32]. Almost a quarter of all SAH patients were treated for a suspected ventriculitis, whereas CSF cultures were only positive in 5%. Patients with a culture-proven bacterial ventriculitis had a longer duration of CSF-drainage and a longer duration of drainage

before clinical suspicion, emphasizing the fact that a bacterial infection needs time to develop and a bacterial ventriculitis is very unlikely to occur within three days after shunt placement[32–35]. We found that no clinical or laboratory features could help to distinguish a bacterial ventriculitis from a sterile inflammatory response. This was also shown in a recent meta-analysis of studies of patients with external ventricular CSF drains who developed drain-associated ventriculitis[36,37]. A recent study on SAH patients did find that a total white blood cell count in CSF was increased in patients with a ventriculitis, but they did not differentiate between a bacterial or sterile ventriculitis[38].

In the absence of a good discriminatory marker clinicians usually start empirically with antibiotic treatment in every suspected case as a CSF culture could take at least three to five days before a definitive result becomes available. But as only a quarter of the suspected cases in our series turned out to have a positive CSF culture, this entails a considerable overtreatment with antibiotics, possibly leading to antibiotic resistance[36]. Better discriminatory tests are therefore needed. PCR on ribosomal DNA seemed a promising technique, but to date has not been proven to aid in the diagnosis of external catheter-associated bacterial ventriculitis[39]. Lactate in CSF and serum procalcitonin, both disturbed in SAH, have also been shown to have limited discriminatory power[40,41]. CSF markers, such as tumor necrosis factor -α, interleukin-1β, interleukin-6 (IL-6), and interleukin-8, have all been shown to increase significantly in patients with an external drain-related bacterial ventriculitis at fever onset, but have not been proven to be useful in daily practice[42,43]. One study of IL-6 in CSF of SAH patients showed a cut-off point of 3100 pg/mL to have an increased likelihood of bacterial meningitis[44]. But overall, studies in IL-6 have shown variable results making implementation into daily practice difficult[36]. CD64 expression on CSF neutrophils seems also a promising new marker which could distinguish between sterile and bacterial ventriculitis in children[45]. A clear cut-off for CD64 has not yet been identified in bacterial meningitis and CD64 has not yet been studied in SAH patients. Most of these new markers have been tested by routine daily sampling. This is not standard practice in SAH-patients as it increases the risk of infection[46]. Therefore, none of these new markers have found their way to the clinic.

In order to prevent external drain-related infections antibiotic-, or silver-impregnated, catheters have been on the market for a while. The evidence of efficacy of these, more expensive, catheters to reduce drain-related infections has been contradictory: some trials support the use of these catheters, but others have not proven a benefit[47–49]. Although a recent multicenter RCT in 1605 patients showed a

reduction in infections in antibiotic-impregnated ventriculoperitoneal shunts (VPS) versus silver-impregnated and standard VPS, shunt failure requiring shunt removal or revision was the same in all groups, querying the true usefulness of these drains[50].

Simple steps to help prevent an infection in the first place have been shown to have an impact in reducing the rate of bacterial ventriculitis. Education in maintenance of CSF catheters for whole teams helps decrease the incidence of bacterial ventriculitis[51,52]. And implementation of a so-called patient care bundle, in which a strict protocol is put in place for the placement, handling and removal of an external ventricular drain, has shown to at least halve the infection rate, sometimes to even as low as 1.2%[51,53,54].

Treatment in poor-grade SAH patients

In **Chapter 4** we investigated the reasons of demise in poor-grade (WFNS grade IV and V) SAH patients in two large treatment centers (Amsterdam and Toronto)[55]. We found that most patients died because of withdrawal of life support (WOLS). Since long, WOLS has been the major reason of demise in critically ill patients in the ICU in general[56]. In recent years, studies have shown that WOLS early in the course of devastating brain injury is associated with early death[57–59]. In cardiac arrest it has even been shown that an early decision to withdraw life support is associated with an added mortality, but that 19% of these patients might have reached a good outcome with prolonged treatment[60]. This study shows, albeit in a different disease, that WOLS in the early course of an illness strongly influences clinical outcome. Possibly, some patients in our cohort, in whom life support was withdrawn, might have reached a good outcome if they had been given more time for recovery. For all patients we found that they died after a median of three days after the initial hemorrhage. Nowadays in critical care medicine, it is generally advised to wait at least 72 hours and to observe the clinical course before making far-reaching decisions regarding a decrease in the intensity of care. If possible, all patients with devastating brain injury, no matter what the cause is, should be resuscitated (both neurologically and in general) aggressively to maximize the chance of a good outcome[58,59]. A study by Laidlaw et al. showed that 30% of all WFNS grade IV and V patients who underwent aggressive aneurysm treatment (within 24 hours) were living independently at three months follow-up[61]. Early treatment, including aneurysm treatment and external ventricular shunt placement, improves outcome and prevent rebleeds in poor-grade SAH patients in other series also[62–64]. Most of these studies, like many others, included WFNS grade IV patients, who are in a significantly better condition at admission: Glasgow Coma

Scale (GCS) score 7-12. The question is what one defines as a poor-grade patient? A GCS score of 12 is a completely different clinical state than a GCS score of 3 and the treatment approach of these patients is completely different. The study described in **chapter 5** shows that an expeditious treatment of even the worst (grade V) SAH patients leads to a better outcome in almost a quarter of patients[65]. Treatment of the causative aneurysm was the strongest related factor associated with this good (GOS 4-5) clinical outcome, despite not preventing more rebleeds in our series. We therefore, hypothesized that the mindset of treating clinicians, i.e. the pro-active approach towards poor-grade patients, resulted in a better outcome. Physicians actively involved in the treatment of a patient will less likely stop treatment once it has been initiated. It seems that if a physician does not believe in a good outcome, it will not suddenly materialize. This nihilism then becomes a self-fulfilling prophecy, leading to a poor outcome[66–68]. Early do-not-resuscitate (DNR) orders have been shown to worsen the outcome in intracerebral hemorrhage (ICH) patients and has an effect on the general medical treatment. DNR orders are often a first step in the continuum of further limitations in care, probably "setting the mind" of the whole team involved in the treatment of the patient[67,69,70]. Therefore, early treatment limitations should be chosen with the utmost care as they strongly influence the outcome of patients[70].

All of us are shaped by our previous experiences. Our upbringing, cultural background, religion and our general belief system have a strong influence on our medical decisions. It leads us to have presumptions about the next case presenting itself and we will act accordingly[71]. When asked, many physicians express doubt over the decision-making process in critically ill patients, as they face an uncertainty what the outcome will be: will aggressive treatment harm or benefit the patient?[72] Expeditious treatment of all poor-grade SAH patients inherently means overtreatment of patients with no realistic chance of meaningful survival. In addition, sparse health care resources will be utilized for these patients which could otherwise have been used for patients with a better chance of recovery. It is pivotal to try and select those patients who have the best chance to benefit from aggressive treatment, but it remains difficult to determine a patient's prognosis from the outset. In **chapter 6** we tried to identify clinical characteristics at admission to help select those WFNS grade V SAH patients who have a good chance of reaching a good clinical outcome and thus would benefit most from treatment. Almost half of the patients presenting with a Glasgow Coma Scale score (GCS) of 3 reached a good outcome. The only significant difference between a poor and good clinical outcome was the presence of bilaterally fixed and dilated pupils. Nevertheless, patients with a good outcome still had bilaterally fixed and dilated pupils in 12% of

the cases[73]. This means that bilaterally fixed and dilated pupils are not a defining characteristic that can be used to abstain from treatment: quite a paradigm shift in neurosurgery! Several prognostic models have tried to improve prediction of the expected clinical outcome. The problem with prognostic models however is, that they are based on decisions already taken in patients on whom the model was based[59,66,74]. External validation of these models will provide evidence if the results of the model can be reproduced in a different cohort (however, the treatment decisions are also made in this external cohort)[75]. A recent prediction model made for early prediction of the outcome in poor-grade SAH, the SAFIRE grade, seems promising[76]. However, it is based on the WFNS after resuscitation, so it is not directly usable at admission but will require intervention(s), like performing an CSF diverting procedure or evacuating an intracerebral hematoma, and thus would not be as useful in helping to decide whether or not to initiate treatment[77]. Most models are also based on a specific time point, whereas a continuum of time points in characteristics and outcome measurements could be more accurate when building a prognostication tool in SAH patients[59,74]. The existing prognostic models for SAH mostly take outcome measures at six or 12 months. A large international multidisciplinary research group recently recommended that long-term outcome should be assessed after 12 months[78]. Longer follow-up is deemed to be too expensive in clinical trials[78], but in 19% of the SAH patients improvement on the modified Rankin Scale Score is seen between the 12 and 36 month mark[64,79].

Are these existing models better than the clinicians' experience? Can we, as doctors, really objectively make a judgment about the chances of a good outcome in patients in a poor condition? In a study performed in ICH patients, it was shown that the clinical judgment of physician and nurses within 24 hours after admission predicted the outcome better than most used prognostication models in ICH[80]. So, physicians hold the questions as well as the answers to aggressive treatment in poor-grade patients: if we believe in good chances for a patient, he or she may have a better chance of survival. We should try not to be fatalistic when faced with an SAH patient in a poor condition as the initial presentation may not be representative of the final outcome. It has been proposed to use the WFNS grade after resuscitation (rWFNS) as it will better predict the outcome in poor-grade patients[81]. However, this implies one should resuscitate all poor-grade patients extensively.

On the other hand, we can be too positive and should therefore, also keep in mind that what a good outcome means for one individual, may not be a good outcome for another, and vice versa. Living a meaningful and worthwhile life is something only a patient and

his or her family can truly be the judge of. And what a person would have thought to be a meaningful life before an episode of serious illness can absolutely change afterwards.

FUTURE DIRECTIONS

Rebleeding still occurs in around 16% of the SAH patients despite the advancements in patient care in the last decades[15]. The evidence for ultra-early aneurysm treatment is still divided[10,12]. A prospective trial of "extra-ultra-early" aneurysm treatment could be worthwhile to be repeated in a 24/7 treatment service in the era of IAT, with treatment aimed to take place within three hours or as soon as possible after the ictus as most rebleeds occur within 2-3 hours after the ictus. This trial will then also answer the question whether ultra-early treatment leads to more periprocedural rebleeds and will lead to a worse outcome. This needs to be compared to a cohort of patients who undergo aneurysm treatment between 3-24 hours after ictus (which is the gold standard nowadays, even though the guidelines still recommend treatment within 72 hours) and aneurysm treatment after 24 hours, with optimum care started directly after admission. Ideally this needs to be set up as a prospective randomized trial. However, in this scenario patients need to be in the hospital within three hours after the ictus before they can be randomized and the group that can be randomized would be too small. A prospective cohort study would be the alternative option to try and answer the question of "extra-ultra-early" aneurysm treatment.

To help shorten the interval between ictus and treatment, studies directed towards improvement and optimization of the pre-hospital logistics are essential. One strategy is to educate the first-responders to recognize an SAH early, enabling getting patients admitted to treatment centers faster. Mobile CT units have been developed, initially to be used bedside in the ICU, but recently also available in ambulances[23,82]. A plain CT of the head in all suspected SAH patients with prompt review by a neuroradiologist via telemedicine should thus lead to a diagnose of SAH as soon as possible. Cost-effectiveness of these mobile stroke units to improve the long-term clinical outcome by getting patients to treatment facilities earlier must then be studied.

The diagnosis of bacterial ventriculitis after SAH is difficult as no clinical or laboratory characteristics can discriminate bacterial from inflammatory ventriculitis. New CSF markers, such as TNF-α, interleukin-1β, interleukin-6 and interleukin-8, have not found their way into the daily practice[33,36]. CD64 in CSF seems promising, but has not been studied in SAH patients. Therefore, a prospective

clinical trial in SAH patients with an external catheter (lumbar or ventricular) with simultaneous sampling for CD64, as well as the regular samples and culture, needs to be conducted. As cell cultures are the gold standard, the results of the CD64 should be compared between culture-positive and -negative patients.

In recent years automated analyzers have become available for counting cells in body fluids and have replaced more manual methods providing earlier and more accurate diagnosis. High-sensitive analysis (hsA) has been developed (Sysmex, Japan) to specifically count cells (white bloods cells, red blood cells and differentiated white blood cells) in CSF. It has been shown to have good accuracy and this could provide a more adequate differentiation in SAH patients with a suspected ventriculitis[83]. SAH patients with an external ventricular catheter could be included in a prospective trial where CSF samples are taken for hsA and routine cultures in SAH patients suspected of a ventriculitis for comparison between patients with a positive and negative culture and patients in a control group.

A major problem with the current studies in poor-grade patients is the mostly retrospective nature. Characteristics, such as the exact neurological condition before resuscitation and the reasons behind treatment decisions, are too frequently not retrievable. Ideally, the benefits of expeditious treatment of WFNS grade V patients needs to be substantiated in a clinical trial in which all patients would be treated aggressively for at least three days before a decision to stop, or to continue, treatment would be made. A trial like that would however, be difficult to set up as it would also involve treatment of moribund patients. A prospective trial in which the characteristics on admission and all treatment decisions are meticulously documented with continuous independent observation and assessment of follow-up during admission is very much needed. Patients in whom more brain stem reflexes are absent other than one or two fixed and dilated pupils would be excluded to prevent treatment of moribund patients. The clinical outcome also needs to be collected at standardized times and in a standardized fashion after discharge. Hopefully, this information will help towards making a better judgment which patients would benefit most from treatment. Potentially a comparative effectiveness study in poor-grade patients in whom, amongst others aggressive treatment and quality of life, is measured will hopefully lead to better decision-making tools for both health care professionals and patients (or proxy)[84].

New prediction models for clinical outcome in WFNS grade V patients before initiation of any form of treatment are necessary. A regression model however does

not take into account changes in one patient during the course of the admission; e.g. what happens to the outcome if a patient develops DCI? Recursive partitioning can create a decision tree in which different time points during the course of the disease can be taking into account[85]. A decision tree will be able to help doctors during admission to predict which outcome group a patient will fall into when events happen to this patient and is less static than a regression model[85].

Quality of life (QOL) after SAH has been extensively researched, but not specifically in poor-grade patients. If a patient returns to independent living the perceived QOL is relatively easy to asses, but in a surviving patient in a poor condition this is no easy task, but one should yield very interesting results. The health-related QOL (HR-QOL) can be obtained even if a patient cannot answer for themselves anymore. The Euro-QOL EQ-5D-5L is a non-disease-specific self-reported HR-QOL measurement which has been investigated in SAH patients[86–89]. It has well established proxy forms in two parts; one in which the caregiver is being asked what they think the HR-QOL of a patient is, and in the second part how they think the patient would report their HR-QOL if they would be able to communicate[89]. The burden on caregivers is an important aspect that needs to be assessed and this can be done via the caregiver Strain Index[90]. About half of the surviving SAH patients experience anxiety and depression and this can also be present in poor-grade patients and should be assessed in patients who can fulfill these questionnaires (hospital anxiety and depression scale)[91–94]. Subtleties that do not come forward in standardized questionnaires, but are important for physicians to explore are whether patients, of whom we think that they have a good outcome, are actually happy to have survived? To get these feelings of patients and their families forward interviews should be performed in a standardized matter using closed questions with yes or no answers[95].

In summary, extra-hospital and in-hospital strategies to prevent rebleeding in SAH need to be further improved, more sensitive CSF measurements to diagnose bacterial meningitis in SAH patients need to be developed, knowledge of the quality of life in surviving poor-grade patients and better differentiation of poor-grade patients who will benefit from aggressive treatment will lead to a better and more meaningful outcome.

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CHAPTER 8:

Summary

SUMMARY

A subarachnoid hemorrhage (SAH) is a devastating disease affecting mostly patients between 50 and 60 years old. It has a significant mortality and morbidity, with 12% even dying before they reach the hospital. Patients who survive the initial ictus can present in a very poor condition, which is associated with a poor outcome in the long term. The condition of a patient at presentation is often graded to estimate the outcome. The most commonly used grading scale is the World Federation of Neurological Surgeons (WFNS) scale, with grade IV and V depicting the patients in the poorest condition. Besides their condition at presentation, every SAH patient is prone to complications which can cause secondary deterioration and thus lead to a poor outcome. The first part of his thesis, chapter 2 and 3, handles with different aspects of complications after SAH which could influence the prognosis; prevention of rebleeds and the time intervals between ictus and treatment and the diagnosis of bacterial ventriculitis after SAH. The second part of this thesis, chapter 4 till 6, describes the different aspects of treatment in patients who present in a poor condition; from the reasons of demise in these patients to the treatment strategy and the patient selection before treatment initiation.

Chapter 2 explores the time intervals from the first symptoms of an SAH to the start of the aneurysm treatment to identify the factors contributing to time delay to treatment. Half of the patients reached a hospital within 169 minutes after the ictus. Three-quarters of the patients underwent aneurysm treatment within 24 hours, with a median interval between hemorrhage and treatment of 17.6 hours. Independent factors contributing to the delay were presentation at a referring hospital (vs. presentation at a treatment center) and admission at a treatment center later in the day. If time can be saved to get patients to the hospital and initiate treatment earlier, rebleeding from the aneurysm and subsequent deterioration and poor outcome could possibly be prevented. The time-intervals between ictus and treatment could be improved upon by direct presentation of an SAH patient at a treatment center and round the clock aneurysm treatment facilities. A “time-is-brain” policy which is proven in ischemic stroke patients could also be applicable to SAH patients.

In **chapter 3** we describe the difficulty to diagnosis a ventriculitis after an SAH. The influx of red blood cells in the cerebrospinal fluid (CSF) caused by the rupture of the aneurysm, causes a sterile inflammatory response which mimics a ventriculitis.

Also, the clinical symptoms of a ventriculitis closely resemble those of an SAH; fever, headache, nuchal rigidity and an altered mental state. Almost a quarter of the SAH patients in our study were, at one time, treated for a clinical suspicion of a bacterial ventriculitis. However, the CSF cultures came back positive in only 5% of the patients. Within the group of patients who were suspected to have a bacterial ventriculitis, only a longer duration of CSF drainage and lower CSF red blood cell counts predicted for culture-positivity. None of the other clinical features or inflammatory indexes in CSF and blood were associated with culture-proven bacterial ventriculitis. New diagnostic methods to differentiate between aseptic and bacterial ventriculitis after an SAH are much needed.

Despite more aggressive treatment in the recent years, a significant number of poor-grade (WFNS grade IV and V) patients still die as a result of the hemorrhage, raising the question of how case-fatality can be reduced. In order to help determine which patients, who present in poor clinical condition, could possibly profit from extensive and invasive treatment after an SAH we determined the reasons of demise in **chapter 4**. In our cohort of poor-grade patients from Toronto and Amsterdam, we found that most patients died with median 3 days after the SAH. Brain dead was the second most common cause of demise in around 15% of the patients. But by far the most common cause of demise was the withdrawal of life-support, which occurred in 71% of the patients. The exact reasons for withdrawal of life support were difficult to retrieve and besides cultural and referral differences between both groups, remain undetermined. This leaves room for the probability that in the whole group of patients in whom life-support is discontinued there are possibly patients who would have had a better prognosis if given more time to recover.

Chapter 5 describes the difference in outcome between two groups of patients presenting in a poor clinical condition (WFNS grade V) in whom different treatment strategies were followed; a conservative treatment approach versus a group in whom patients were treated aggressively. Expeditiously treated patients had a good outcome in 22% versus 11% of the patients who were treated in a more conservative matter. Aneurysm occlusion and external ventricular catheter placement were both highly associated with a good outcome. Aneurysm occlusion was the only variable that remained significant in a multivariate model (OR (95% CI) of 43.73 (10.34-184.97)). However, patients in the expeditiously treated group did not experience less rebleeds than the patients in the conservative group. So, if aggressive treatment

does not prevent rebleeds, the observed better outcome is most likely attributable to a different mindset. Once treatment is initiated physicians are less likely to discontinue treatment, thus giving patients more time to improve. Hesitance in the early stages based on doubt about realistic chances of a meaningful recovery seems to be a self-fulfilling prophecy for a poor outcome.

When aggressive treatment improves the outcome, which patients would benefit most from this approach? As an expeditious treatment not only improves the outcome but as a downside also causes more patients to survive in a poor condition as seen in **chapter 5**. We evaluated the disease-related characteristics, present at admission, which could possibly identify patients with a chance of a good outcome in **chapter 6**. In our study all patients who did not undergo aneurysm treatment died. A third of the treated patients reached a good outcome, almost half (47%) of them presented with a Glasgow Coma Scale (GCS) of 3 and half had pupillary abnormalities, four even had bilaterally fixed and dilated pupils. So reliable identification of patients who would benefit from treatment seems difficult, as symptoms like fixed and dilated pupils or a low GCS do not discriminate enough.

In **chapter 7** the results from this thesis are discussed together with future directions for research. We discuss the extra-hospital and in-hospital strategies to prevent rebleeding in SAH which need to be further improved and possible methods for more sensitive CSF measurements to diagnose bacterial meningitis in SAH patients. The knowledge of the quality of life in surviving poor-grade patients and better differentiation of poor-grade patients who will benefit from aggressive treatment will hopefully lead to a better and more meaningful outcome in the poor-grade patients.

CHAPTER 9:

Samenvatting

SAMENVATTING

Een subarachnoïdale bloeding (SAB) is een zeldzame vorm van een hersenbloeding, waarbij het bloed zich, voornamelijk, tussen de hersenvliezen bevindt. Dit wordt meestal veroorzaakt door een gebarsten aneurysma van de grote hersenvaten. Een SAB is een ernstige aandoening die, meestal, patiënten treft tussen de 50 en 60 jaar oud. Het beloop na een bloeding gaat gepaard met een hoge mortaliteit en morbiditeit, 12% van de patiënten overlijdt zelfs al voordat zij het ziekenhuis bereiken. Een deel van de patiënten die de initiële bloeding (ictus) overleven presenteert zich in een slechte neurologische conditie, deze slechte conditie is geassocieerd met een slechte uitkomst op de lange termijn. De neurologische conditie bij binnenkomst in het ziekenhuis wordt meestal gescoord op basis van verschillende schalen. Eén van de meest gebruikte is de World Federation of Neurological Surgeons (WFNS) gradering, waarbij graad IV en V de patiënten in de meest slechte conditie beschrijft. Naast een slechte neurologische conditie bij binnenkomst lopen SAB-patiënten een risico op secundaire complicaties welke de uitkomst op lange termijn negatief kunnen beïnvloeden. Het eerste deel van dit proefschrift, hoofdstuk 2 en 3, behandelt verschillende aspecten van complicaties na een SAB: het voorkomen van een hernieuwde bloeding (rebleed) en de tijdsintervallen tussen de ictus en de behandeling en de diagnostiek van een bacteriële hersenvliesontsteking (meningitis) na een SAB. Het tweede deel van dit proefschrift, hoofdstuk 4 tot en met 6, gaat over verschillende aspecten van de behandeling van SAB-patiënten die zich in een slechte neurologische conditie presenteren; van de reden van overlijden van deze patiënten tot de behandelstrategie en de selectie van patiënten die het meeste baat hebben bij een behandeling.

In **hoofdstuk 2** worden de tijdsintervallen tussen de eerste symptomen van een bloeding en de start van een aneurysmabehandeling bekeken en de factoren die de tijd tot de behandeling kunnen vertragen. De helft van de patiënten in deze studie bereikten een ziekenhuis binnen 169 minuten na de ictus. Driekwart van de mensen onderging een aneurysmabehandeling binnen 24 uur, met een mediaan interval tussen bloeding en behandeling van 17,6 uur. Onafhankelijke factoren die ervoor zorgen dat een aneurysmabehandeling vertraagd wordt zijn presentatie in een verwijzend ziekenhuis (in plaats van directe presentatie in een behandelcentrum) en opname in een behandelcentrum op een later moment op de dag. Het is mogelijk dat, als een patiënt eerder in een behandelcentrum gepresenteerd wordt en de aneurysmabehandeling eerder kan plaatsvinden, rebleeds en de daardoor veroorzaakte verslechtering voorkomen kunnen worden. Directe presentatie in een

behandelcentrum en de mogelijkheid om 24 uur per dag aneurysmabehandelingen uit te voeren zouden de tijdsintervallen tussen ictus en behandeling kunnen verbeteren. Een “time-is-brain” strategie, welke bekend en beproefd is bij de behandeling van het herseninfarct, kan ook toepasbaar zijn bij SAB-patiënten.

In **hoofdstuk 3** beschrijven wij de lastige diagnostiek van een bacteriële meningitis na een SAB. De instroom van rode bloedcellen in de ruimte van het hersenvocht (liquor) veroorzaakt door de ruptuur in het aneurysma zorgt voor een steriele ontstekingsreactie welke zeer sterk lijkt op een meningitis, een zogenaamde aseptische meningitis. Bovendien hebben de klinische symptomen van een meningitis veel gelijkenis met de symptomen van een SAB; koorts, hoofdpijn, nekstijfheid en een verminderd bewustzijn of verwardheid. Bijna een kwart van de SAB-patiënten wordt, op enig moment tijdens hun opname, behandeld voor een verdenking op een bacteriële meningitis. Echter slechts bij 5% van alle patiënten is er sprake van een positieve liquorkweek (de gouden standaard voor de diagnostiek van een meningitis) voor bacteriën. Dit betekent dat veel patiënten mogelijk overbehandeld worden met antibiotica. Binnen de groep van patiënten die verdacht zijn voor een meningitis waren alleen een langere duur van liquordrainage en een lager aantal rode bloedcellen in de liquor voorspellend voor een positieve liquorkweek. Geen van de andere klinische symptomen of waarden in het bloed of de liquor bleken geassocieerd te zijn met een positieve liquorkweek. Nieuwe diagnostische methoden om te kunnen differentiëren tussen een aseptische meningitis en een bacteriële meningitis na een SAB zijn noodzakelijk om gerichtere behandeling te kunnen geven en overbehandeling met antibiotica te voorkomen.

De laatste jaren is het steeds gebruikelijker om SAB-patiënten in een slechte conditie (WFNS-graad IV en V) laagdrempeliger te behandelen, maar desondanks overlijdt nog steeds een significant deel van deze patiënten. Hoe kan deze mortaliteit verminderd worden en zitten er in de groep van patiënten die overlijden alsnog patiënten die zouden kunnen overleven als ze intensiever behandeld zouden worden? Als eerste stap om deze vraagstellingen te beantwoorden onderzochten wij in **hoofdstuk 4** de reden van overlijden in patiënten met een WFNS-graad IV en V na een SAB. In SAB-patiënten uit Toronto en Amsterdam vonden wij dat de meeste patiënten mediaan 3 dagen na de SAB kwamen te overlijden. Hersendood was de tweede oorzaak van overlijden, in totaal werd in 15% van de patiënten de hersendood vastgesteld. Maar verreweg de meeste patiënten overleden omdat de ondersteunende behandeling gestaakt werd bij een verwachte infauste prognose.

Dit was het geval in 71% van de patiënten. De exacte reden waarom de behandeling gestaakt werd en de prognose infaust geacht werd waren lastig terug te vinden. Hierdoor zou het kunnen zijn dat er in deze groep patiënten zijn die mogelijk zouden profiteren van een meer intensieve behandeling en dat er patiënten zouden kunnen zijn die opknappen als zij meer tijd zouden krijgen om te herstellen.

Hoofdstuk 5 beschrijft de verschillen in uitkomst tussen twee groepen van SAB-patiënten in een slechte conditie (WFNS-graad V) waarbij een verschillende behandelstrategie werd gevolgd; agressieve behandeling versus een meer conservatieve en afwachtende behandeling. Agressief behandelde patiënten bleken een goede uitkomst te hebben in 22% van de gevallen, tegenover 11% van de patiënten die meer afwachtend benaderd werden. Behandeling van het aneurysma en het plaatsen van een externe ventrikel drain bleken allebei sterk geassocieerd met een goede uitkomst. Aneurysmabehandeling (zowel endovasculaire coiling als chirurgisch clippen) was de enige variabele die significant bleef in een multivariaat model (OR (95% CI) of 43.73 (10.34-184.97)). De agressief behandelde patiënten bleken echter niet minder rebleeds door te maken dan de conservatief behandelde patiënten. Dus als agressieve aneurysma behandeling niet leidt tot een minder rebleeds dan is de betere uitkomst wellicht te wijten aan een andere mind-set van de behandelaren. Als agressieve behandeling eenmaal is ingezet is de drempel om deze op korte termijn te staken waarschijnlijk hoger en wordt daarmee de patiënten meer tijd gegeven om op te knappen. Twijfel over een goede uitkomst in de vroege fase na een SAB lijkt een “self-fulfilling prophecy” (je krijgt wat je verwacht) voor een slechte uitkomst.

Als een agressieve behandeling de uitkomst verbetert en een groot deel van de patiënten overlijdt doordat ondersteunende behandeling gestaakt wordt, hoe selecteer je dan de patiënten die kunnen profiteren van een intensieve behandeling? Een agressieve behandeling zorgt immers niet alleen voor een betere uitkomst in een deel van de patiënten, maar het bleek uit het onderzoek in **hoofdstuk 5** dat een agressieve behandeling ook zorgt voor overleving van patiënten in een matige tot slechte conditie. In **hoofdstuk 6** werden de ziekte- en patiënt-gerelateerde karakteristieken van WFNS-graad V patiënten die aanwezig zijn bij opname bekeken om mogelijke kenmerken te identificeren die aanwijzingen kunnen geven voor een goede uitkomst. Alle patiënten die niet behandeld werden kwamen te overlijden. Een derde van alle patiënten die wel een behandeling van hun aneurysma ondergingen hadden een goede uitkomst; bijna de helft (47%)

presenteerde zich met een Glasgow Coma Scale (GCS) score van 3. Ook had bijna de helft van de patiënten met een goede uitkomst afwijkende pupilreflexen bij binnenkomst, vier patiënten hadden zelfs beiderzijds wijde en lichtstijve pupillen. Betrouwbare herkenning van patiënten die zouden kunnen profiteren van een agressieve behandeling lijkt lastig, aangezien symptomen als een lage GCS en wijde lichtstijve pupillen niet genoeg blijken te differentiëren.

In **hoofdstuk 7** worden de resultaten van dit proefschrift bediscussieerd en de richting voor toekomstig vervolgonderzoek uiteengezet. De strategieën binnen en buiten het ziekenhuis om rebleeds te voorkomen kunnen verbeterd worden door bijvoorbeeld eerdere diagnostiek. Gevoeligere methodes om in de liquor van patiënten met een SAB een meningitis vast te stellen zijn veelbelovend. Kennis over de kwaliteit van leven in patiënten die een SAB overleven en zich in een slechte conditie presenteerden en een betere herkenning van welke van deze patiënten het meeste baat hebben bij een agressieve behandeling leidt hopelijk tot een betere en een meer betekenisvolle uitkomst.

APPENDICES

List of abbreviations
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LIST OF ABBREVIATIONS

AMC	Academic Medical Center
aSAH	aneurysmal subarachnoid hemorrhage
AUMC	Amsterdam University Medical Centers
CI	confidence interval
CRP	C-reactive protein
CSF	cerebrospinal fluid
CT	computed tomography
CTA	computed tomography angiography
DCI	delayed cerebral ischemia
DNR	do-not-resuscitate
DSA	digital subtraction angiography
EVC	external ventricular catheter
ELD	external lumbar drainage
EVD	external ventricular drainage
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
H&H	Hunt and Hess
HR-QOL	health-related quality of life
hsA	high-sensitive analysis
IAT	intra-arterial treatment
ICH	intracerebral hemorrhage
ICP	intracranial pressure
ICU	intensive care unit
IL-6	interleukin-6
IQR	interquartile range
LOC	loss of consciousness
LP	lumbar puncture
mRS	Modified Rankin scale
MSU	mobile stroke unite
NPE	neurogenic pulmonary edema
OR	odds ratio
PAASH	Prognosis on Admission of Aneurysmal Subarachnoid Hemorrhage
QOL	quality of life
RBC	red blood cells
SAH	subarachnoid hemorrhage

SD	standard deviation
SDD	selective decontamination of the digestive tract
SMH	St. Michael's Hospital
T_{max}	daily maximum temperature
TXA	tranexamic acid
ULTRA	ultra-early tranexamic acid in subarachnoid hemorrhage
UMCU	University Medical Center Utrecht
VPS	ventriculoperitoneal shunt
VUmc	VU University Medical Center
WBC	white blood cells
WFNS	World Federation of Neurological Surgeons
WOLS	withdrawal of life support

PhD PORTFOLIO

Name PhD student:	Jantien Hoogmoed
PhD period:	2009-2020
Name PhD supervisor:	prof. dr. W.P. Vandertop

	Year	Workload (ECTS)
General courses		
- Active learner	2009	0,25
- BROK	2012	1
- Quality Assurance and Quality Control in Clinical Research	2016	0,25
Specific courses		
- NVNA training course neurovascular surgery, Utrecht	2010	0,5
- ECNR:Embryology/Anatomy/Malformations/ Genetics, Taragona	2010	1
- EANS training course: Vascular, Prague	2013	1
Seminars, workshops and master classes		
- Advances in neurovascular diseases, Leiden	2011	0,5
- NICA symposium, Amsterdam	2014	0,25
- 8th Conference Course of the Dutch Society of Neuroradiology, Amsterdam	2012	0,25
Presentations		
- Scientific presentation AMC Neurosurgery	2008-2020	3
- Oral presentation NVVN wintermeeting, Utrecht	2012	0,5
- Poster presentation at Annual meeting Amsterdam Neuroscience	2018	0,5
- Oral presentation EANS Vascular meeting, Nice	2018	0,5
(Inter)national conferences		
- ABC-WIN, Val d'Isere	2013	1,25
- ABC-WIN, Val d'Isere	2014	1,25
- EANS Vascular meeting, Nice	2018	0,5
Other		
- Weekly journal club AMC neurosurgery	2009-2020	12
- Biweekly research meeting AMC	2014-2020	7

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CURRICULUM VITAE

Jantien Hoogmoed was born on August 3rd, 1980 in Zaanstad. She grew up as an only child in the small village of Jisp. In 1998 she graduated from the Sint Michaël College (VWO) in Zaandam and was admitted to medical school the same year. She obtained her additional VWO certificates in Biology, Chemistry and Physics at the Regio College in Zaandam in 1999 after which she started studying at the University of Amsterdam. During medical school she took a little time off to work, travel and drive old-timer car rally's which took her, amongst others, to the Sahara desert. After graduating medical school in 2008, she started her neurosurgery residency in December 2008 at the Academic Medical Center (AMC) in Amsterdam (prof. dr. W.P. Vandertop). During her residency she started her PhD research under supervision of prof. dr. W.P. Vandertop and co-supervisors dr. D. Verbaan and dr. B.A. Coert. As part of het residency program she worked 6 months in the VUmc (prof. dr. S.M. Peerdeman) and 6 months in the Onze Lieve Vrouwe Gasthuis (dr. G.J. Bouma). She developed a special interest in endoscopic skull base surgery during her training. After finishing her residency she stayed on at the AMC as a staff member with focus on pituitary and endoscopic skull base surgery. She's also part of the management team of the AMC Neurocenter. Jantien lives in Amsterdam with Patrick Klein Bog and their daughter Noortje.