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Comatose patients in the non-traumatic emergency room:

Clinical findings, etiologies and prognosis

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ABSTRACT

A reduced level of consciousness is an acute and life threatening condition that requires a rapid and structured management in order to maintain life and brain function. Unconscious patients admitted to the non-traumatic emergency room thus present a major challenge to physicians. The scientific knowledge in the field is limited.

The aims of this thesis were to improve the knowledge of underlying etiologies to coma and their short and long term prognosis, and to search for clinical tools to facilitate the diagnostic procedure.

The findings reported in this thesis are mainly based on a cohort of prospectively included patients admitted unconscious to hospital during the years 2003-2005. A complementary cohort consists of poisoned patients consecutively admitted to hospital during the years 2009 through 2010.

Poisoning was the most common cause of unconsciousness in the non-surgical emergency room (38%) and young age was a strong predictor of this condition (80% of the comatose patients with an age below 40 consisted of poisonings).

Around one third of all hospitalized poisonings had a pronounced central nervous system depression on admission. The mortality rate among poisonings presenting unresponsive was found to be at least five times higher than the overall mortality from acute poisoning.

The acute prognosis in patients presenting comatose to the emergency room was shown to be serious and dependent on both coma etiology and depth of coma. The overall hospital mortality was 26.5%. Long term prognosis among he hospital survivors was strongly correlated to the coma etiology, with 2-year mortality rates ranging from 11.5% for poisonings to 83% for malignancies, but was not influenced by the initial Glasgow coma scale score. Overall, the prognosis was much more favourable for the coma etiologies poisoning and epilepsy.

A composite of age, systolic blood pressure and results of a routine neurological examination could be shown to validly discriminate between the two underlying causes of consciousness disturbances, namely those of metabolic or focal origin. From the data obtained, the following diagnostic algorithm may be formulated:
If a patient is younger than 51 years of age, and his or hers systolic blood pressure on admission is below 151 mm Hg, and no neurological findings indicative of a discrete lesion within the central nervous system is present, then the statistical probability of an underlying metabolic coma is 96%.
If the algorithm presented above were to be applied routinely in the emergency room, the numbers of emergency CT scans could be considerably reduced. Consequently, other potentially life saving procedures would achieve a higher priority in the emergency room.

Key words: coma, differential diagnosis, emergency medicine, mortality, neurological examination, prognosis, unconsciousness
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LIST OF PUBLICATIONS

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Metabolic versus focal coma in the emergency department –an observational study.
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IV. Forsberg S, Höjer J, Ludwigs U.
Hospital mortality among poisoned patients presenting unconscious
Submitted

CONTENTS

LIST OF ABBREVIATIONS

ARAS	Ascending Reticular Activating System
CBF	Cerebral blood flow
CI	Confidence intervals
CNS	Central nervous system
CO	Cardiac output
CPC	Cerebral Performance Category
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
ECG	Electrocardiogram
EEG	Electroencephalogram
ER	Emergency room
GCS	Glasgow Coma Scale
HR	Hazard ratio
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
OR	Odds ratio
RLS 85	Reaction level scale 85
SD	Standard deviation

1 INTRODUCTION

The management of unconsciousness patients who are unable to communicate constitute a major challenge to the emergency physician.

1.1 HISTORICAL BACKGROUND

Archaeological evidence of the occurrence of the surgical procedure of trepanation as early as 6000 years ago illustrates that a link between brain and consciousness has been known or suspected for a very long time. This has been documented from pre-Columbian Peru to bronze-age Europe and Neolithic Africa (1-3).

During the period of the 6th to 4th century BC, Greek philosophers and physicians such as Alcmaeon, Hippocrates and Plato postulated a correlation between sensations and the brain (4). This theory of encephalocentrism considered the brain to be the centre of consciousness, sensation and knowledge. A rival theory of cardiocentrism, put forth by Aristotle and others, considered the heart to be the origin of these faculties. Both theories were maintained and the dichotomy between the two continued well into the renaissance period. As late as the 17th century, William Harvey, the English physician who discovered circulation, wrote that "the heart has to be source of sensitive, motor and vegetative life (4).

In the end of the 19th century, it was proposed by neurologist John Hughlings-Jackson that consciousness resided in both cerebral hemispheres and that unconsciousness could only be present if both hemispheres were damaged simultaneously (5). From this time, more and more reports discussed the brain and brainstem in the context of consciousness. The opinion of Hughlings-Jackson was challenged by several clinical observations. Mauthner reported that stupor among patients with Wernicke's encephalopathy was associated with lesions in the grey matter around the cerebral aqueduct and the third ventricle (5).

Loss of consciousness was also associated with lesions in the upper brainstem and diencephalon. The most convincing observations were made by the Austrian neurologist Baron Constantin von Economo, who described impaired consciousness and brain stem reflex abnormalities during an epidemic disorder (encephalitis lethargica) around the time of the

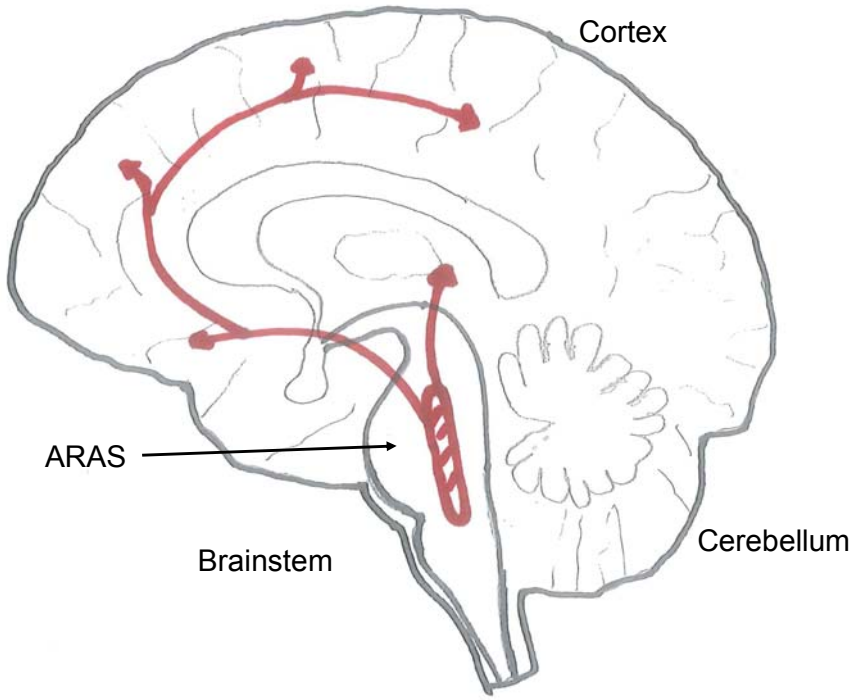
First World War. The symptoms had correlations to lesions found in the paramedian reticular formation in the midbrain towards the diencephalon and in the grey matter anterior to the third ventricle in the hypothalamus and extending laterally into the basal ganglia. Von Economo proposed that this specific circuitry in the brainstem caused wakefulness and arousal of the forebrain. Another circuit in hypothalamus was suggested to be inhibitory and induce sleep. These hypotheses were difficult to prove, because naturally occurring lesions in patients or experimental lesions in animals destroyed too much of the important pathways (6).

After World War II, Moruzzi and Magoun created selective midbrain lesions in cats leading to different results on consciousness (6-8). These observations emphasised the midbrain reticular core to be important for arousal, and the pathways involved were called the ascending

reticular activating system (ARAS). However, it was not until the 1970s and 1980s that experiments clarified the nature of the pathways with two major branches originating from cell groups with identified specific neurotransmitters. The first branch originates from acetylcholine-producing cell groups in the upper brainstem that activate thalamic relay neurons which are crucial for transmission to the cerebral cortex. The second branch originates from

monoaminergic neurons in the upper brainstem and caudal hypothalamus. Activation of the second branch bypasses the thalamus bypasses the thalamus on its way to the brain cortex (6, 8, 9) (Figure 1).

Figure 1. *The ARAS. For a subject to remain conscious, it is necessary that efferent input can be*



transmitted through the pathways of an intact ARAS. The ARAS consists of several structures in the upper brainstem and signals from the system are projected to the cortex through two different pathways. The first one reaches cortex through the thalamus by a dorsal tract and the second ventral pathway passes mainly through the hypothalamus in the forebrain.

The findings of von Economo in the beginning of the 20th century have led to a better understanding how lesions in the region of the ARAS lead to impaired consciousness.

1.2 SCIENTIFIC BACKGROUND

Even today, unconscious patients represent a clinical problem in the medical emergency room (ER). Around one percent of patients admitted to the ER are unconscious (10, 11). Many different conditions may have impact on brain function and thereby cause impaired consciousness or coma. The reasons may be trauma to the head with intracranial bleeding and swelling of the brain, or may be medical conditions such as atherosclerosis, hypertension, metabolic disorders, malignancies, respiratory failure or intoxication. They may also be of psychogenic nature. Nevertheless, it is important to clarify the reason for impaired consciousness, and if possible, to treat it as soon as possible before permanent brain damage has occurred. Thus, patients presenting with coma of unknown etiology constitute a high-risk group requiring instant management and often extensive diagnostic procedures, such as lumbar puncture, blood cultures, administration of different antidotes, and computed tomography (CT) of the brain.

In spite of this, systematic studies of patients presenting in the ER with unconsciousness are surprisingly few. A literature search (1958-2011) for publications in which consecutive comatose

patients have been identified and followed up resulted in no more than three relevant citations (11-13)

Kanich et al. studied (2002) the etiologies responsible for altered mental status in a mixed ER population (including trauma) of 317 patients. In their opinion, for diagnostic purposes, history and clinical examination were more important than laboratory studies. They found that ER resource use was high. Hospital mortality was only 9%. However, not only unconscious but also patients with various kinds of changes in mental status were included (11).

In 1981, Levy et al. published a widely cited paper on prognoses in coma (12). Patients whose coma was caused by trauma or drugs were excluded. 500 patients were identified during the years 1973 to 1977 with an impaired consciousness corresponding to a GCS score of 8 or less. They were followed for a 1-year period. Sixteen % of the patients led an independent life at some point within the first year; the remainder died without recovery from coma (61%), or remained dependent on others for daily activities, either conscious or in a vegetative state. Overall mortality at twelve months was 88%. Prognosis was to some degree related to the cause of coma (cerebrovascular disease had the worst prognosis and hepatic and miscellaneous causes the best) and especially to early clinical signs of brain dysfunction. Sacco et al. (1990) prospectively studied Glasgow coma score and coma etiology as predictors of 2-week outcome in 188 non-traumatic coma patients with GCS score of eight or less (13). Both etiology and initial GCS-score level correlated to outcome. Eighty-five percent of the patients with an initial GCS score of 3 to 5 were either dead or in persistent coma at two weeks. If initial GCS score was 6-8, 47% were dead or in persistent coma. Hypoxic or ischemic coma had the worst 2-week outcome (79% dead or comatose) while drug-induced coma had a better prognosis (27% dead or comatose).

1.3 GENERAL ASPECTS OF IMPAIRED CONSCIOUSNESS

1.3.1 Definition of consciousness

Consciousness in the human being may be an ambiguous concept and is sometimes difficult to define, but it includes a fully awake state and awareness of the self and the environment. The two terms arousal and awareness describe the different parts of consciousness that interact in the human. Both arousal and awareness have to be without impairment for the patient to be fully conscious. If not, there is some degree of impaired consciousness (8, 14-17).

Arousal. This term tells us at what level of wakefulness the subject is and if there is reaction to different kind of stimuli. It does not include the accuracy of the response. Healthy individuals normally show different levels of arousal, from deep sleep to fully awake or aroused. Decreased levels of arousal (such as during sleep) from which the subject can be aroused and then maintained awake represents normal variations of wakefulness.

Awareness, or content of the patients experience includes all sensations, emotions, imaginations or anything that stimulate the individual. The processing of these stimuli in the human central nervous system influences the level of consciousness. The awareness may be compromised in several ways as discussed below.

1.3.2 Terminology and quantification of the level of unconsciousness

The severity of alterations in the mental state ranges from only slight impairment to complete unresponsiveness. Before the 1970:s these changes in levels of consciousness were expressed in descriptive terms that lacked rigorous definitions leading to problems of communication both in

clinical practice and in the scientific literature (5, 18-21). The terminology used may be summarised as follows:

- *Clouding of consciousness* implies only minor changes from normal, such as hyperexitability or drowsiness. The patient may be incompletely orientated in time.
- *Delirium* means that the patient is disorientated both to time and place. They may not recognise well known faces but usually retain the knowledge of the self.
- With *Obtundation*, the patient is blunted and has a reduced alertness and low interest in the surroundings.
- *Stupor* means that the patient is in deep sleep, but can be aroused with continuous stimulation. He will immediately fall back to sleep when stimulations stops. Even with maximal stimulation the patient will not be completely aware.
- In *Coma*, the patient is in deep sleep and can not be aroused by any degree of stimulation.

1.3.3 Scoring systems

A scoring system that is easy to use and interpret may be regarded as the simplest, least expensive and most reliable tool to assess and monitor the neurological course in patients admitted due to alterations of consciousness. An ideal scoring system should by easy to use, be valid for all patients, accurately assess the level of compromised consciousness, quickly identify deterioration and reliably predict morbidity and mortality. Such a system does not exist but several scoring methods have been proposed and compared against others.

Teasdale and Jennet choose to examine eye opening, verbal response and motor response. Their work resulted in the most widely used coma score, the Glasgow Coma Scale that was first introduced in 1974 (22) and modified a few years later to its present form (23), Table 1.

Table1. The Glasgow Coma Scale

Eye opening	Best verbal response	Best motor response
1 = none	1 = none	1 = none
2 = to pain	2 = incomprehensible	2 = extending
3 = to sound	3 = inappropriate	3 = flexing
4 = spontaneous	4 = confused	4 = withdrawing
	5 = orientated	5 = localizing
		6 = obeying commands

The GCS was initially intended to be used after traumatic brain injury in the neurosurgical intensive care unit to facilitate monitoring and communication about the patients but has also proven to be a useful tool for prediction of outcome in intracranial haemorrhage, poisoning, neurodegenerative disease, cardiac arrest and meningitis just to mention a few conditions. The reaction level scale (RLS85) was formulated to overcome the shortcomings of the GCS, ie the difficulty of its use in intubated patients and in patients with swollen eyelids. The RLS scale is based on the same objective assessments as GCS but the separate modalities are combined. The

RLS85 is organized in eight possible levels where 1 denotes completely conscious and 8 deep unconsciousness or unresponsiveness, Table 2 (24).

Table 2. *The Reaction Level Scale 85*

Grade	Reaction
1	Alert, no delay in response
2	Drowsy or confused
3	Very drowsy or confused
	Mentally responsive 
	Unconscious 
4	Localizes pain
5	Withdrawing on pain stimulation
6	Stereotype flexion on pain stimulation
7	Stereotype extension on pain stimulation
8	No response on pain stimulation

RLS 4-8 is comparable to a GCS score of 8 or below.

As GCS, the RLS85, was initially tested and evaluated in the neurosurgical setting and has been evaluated against the GCS by several investigators (19, 25, 26). The RLS85 was shown to be superior to GCS in predicting outcome (27, 28). The main disadvantage of RLS85 is that its use is mostly limited to Sweden (25). The RLS85 is therefore not suitable for comparative purposes in scientific studies of unconscious patients.

Other alternatives to GCS have been proposed. The Innsbruck coma scale (29), a 23 point scale, the Edinburgh-2 Coma Scale (E2CS) (30) which can not be used in patients unable to give a verbal response and the Advanced Trauma Life Support AVPU scale (Alert, response to Verbal and Painful stimuli, Unresponsive).

To incorporate brainstem reflex function when evaluating patients in coma, Wiejdicks and others recently proposed a new scale, the Full Outline of Unresponsiveness (FOUR) that includes four components; eye, motor, brainstem and respiratory functions (31).

However, the GCS is the golden standard against which newer scales are compared. More than 4 500 publications referenced the GCS paper in 2005 and the scale been incorporated into several other scoring systems as the Acute Physiological and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS) (19, 25).

1.4 DIFFERENTIAL DIAGNOSIS OF THE UNCONSCIOUS PATIENT

1.4.1 Medical history

Although by definition the unconscious patient is unable to give a medical history herself, prompt gathering of information from other sources is of utmost importance. These may include relatives, ambulance personnel or pre-existing medical records.

1.4.2 Physical examination

A structured approach is important in the management of the unconscious patient. The ABCDE concept has been widely adopted for this purpose and its use increases the likelihood that patency of the airway (A), adequacy of breathing (B) and circulation (C) and signs of neurological disability or disorder (D) are promptly checked for in the acute situation. Looking for signs of exposure (E) include measuring body temperature and inspecting the skin for needle marks and signs of overt trauma, discolouration, icterus and petechiae (32-34). It is also of importance to detect odours indicative of intoxication or organ failure. In the following sections, details pertinent to the physical examination of the different organ systems are discussed.

1.4.2.1 Respiration (35)

The brain is very sensitive to hypoxia and cerebral function will decrease within seconds. Normal respiration is maintained through a chain of interactions where every link must be intact. This chain includes normal central nervous system, normal spinal cord, normal neuromuscular function, normal thorax aperture, normal large and small airways and normal circulation. A disruption in any link, in this chain, might influence the adequacy of respiration.

Breathing frequency, normally 12-16 per minute and breathing pattern should be registered in in the ER. Tachypnea is an unspecific sign that may be present in a vast number of underlying pathological conditions. An increase in breathing frequency usually precedes a fall in blood pressure during the development of circulatory chock.

Bradypnea, on the other hand, is usually due to inhibition of the medullary respiratory centre, either by drugs such as opiates or sedatives or by hypothermia. Intermittent monitoring of breathing frequency in unconscious subjects is important to follow the course of the underlying illness.

The pattern of breathing, if abnormal, may give important clues to the underlying condition. Kussmaul breathing in metabolic acidosis, Cheyne-Stokes respiration in CNS disturbances or circulatory or pulmonary dysfunction, Biots agonal respiration and hyperventilation secondary to drug effects on the respiratory centre such as salicylic acid and theofylline are examples of abnormal breathing patterns.

1.4.2.2 Circulation (36)

Adequate blood perfusion is necessary for the supply of oxygen and nutritients to the brain. Under normal conditions, cerebral blood flow (CBF) constitutes 15-20 % of the cardiac output (CO) (37). It remains relatively constant but regional changes occur to meet metabolic demands in different regions of the brain (38). Overall blood flow in grey brain matter is three to four times higher than in white matter (39). The autonomic nervous system adjusts the blood pressure through a balance between sympathetic tone which increases heart rate and stroke volume and thereby the CO and parasympathetic tone that lowers heart rate when stimulated. In the ER, blood pressure and heart rate can be measured but the cerebral perfusion pressure (CPP) can only be estimated. Normally, the cerebral perfusion remains stable over a wide range of blood pressure (40, 41). When the mean arterial pressure (MAP) is too low or too high, the autoregulation fails to maintain adequate cerebral perfusion, Figure 2. In such situations, prompt measures must be taken to increase or decrease blood pressure to levels compatible with cerebral circulation homeostasis (37, 42-44).

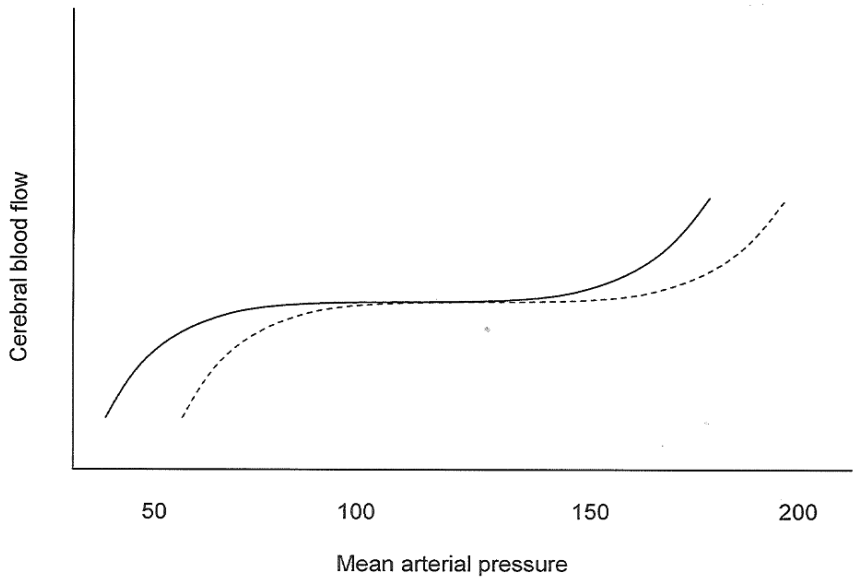


Figure 2. *Cerebral autoregulation in normal subjects, solid line, and in hypertensive patients in dashed line. In both situations the autoregulation will maintain the CBF over a wide range of mean arterial pressure.*

1.4.2.3 Neurology (5, 45, 46)

Examination of the pupils

The pupillary light reflex is easily and rapidly tested. The reflex is balanced by sympathetic (dilatation) and parasympathetic (constriction) pathways intertwined with parts of the ARAS. The reflex is tested with direct and indirect light and with pain stimuli. Both pupils should contract on light and dilate on pain stimuli. Small reactive pupils indicates opiate overdose or may be caused by certain metabolic causes of unconsciousness. Pinpoint pupils indicate a pons lesion and normal size unreactive pupils indicate a midbrain lesion or brain death. Unilateral pupil dilatation with slow or absent light reaction indicate ipsilateral compression of the oculomotor nerve, usually by a tumour or bleeding (Hutchinson's pupil). The physician should be aware of that around 10% normally have anisocoria (47).

Oculomotor responses

Brainstem nuclei and pathways that control eye movements lie close to the ARAS and their function is important to test in unconscious patients. In metabolic disorders eye movements will typically be conjugate whereas asymmetric reactions are typical of structural lesions. By rotating the head from one side to the other and up and down, the vestibulo-ocular responses are tested. Normal responses imply intact brain stem pathways which is unusual in structural cause of unconsciousness.

Motor responses (skeletal muscle activity)

Motor responses are tested for voice stimuli. Asymmetrical motor response is highly indicative of a structural lesion. If no response is registered, a painful stimulus is used to further characterise the level of damage. Decorticate posturing consists of adduction of the upper arms, flexion of the lower arms, wrists and fingers. The lower extremities extend in decorticate posturing. Decerebrate posturing consists of adduction of the upper arms, extension and pronation of the lower arms, along with extension of the lower extremities.

Motor reflexes
Deep tendon reflexes in drowsy patients may be hyperactive but are reduced or disappear with deeper coma. Unilateral extensor plantar reflex (the Babinski sign) implies injury to the contralateral descending corticospinal tract. A bilateral extensor reaction is unspecific and a common finding in states of compromised consciousness.

Motor tone
Normal muscle tone offers a mild resistance when tested. Superficial alterations in mental state often results in an increased muscle tone. With deeper coma, muscle tone is markedly reduced and may be completely absent.

1.4.3 Diagnostic procedures

In the ER, it is imperative to test for conditions where rapid interventions may be lifesaving in the unconscious patient. An electrocardiogram (ECG) must be registered as early as possible and will give clues about electrolyte disturbances, intoxications with membrane stabilizing agents or indicate primary cardiac disorders such as coronary insufficiency or arrhythmia (45, 48).

1.4.3.1 Blood chemistry
On site assays for blood levels of glucose, sodium and calcium should be performed as early as possible. Often, these results are acquired from a single arterial blood sample that is also used for analysis of blood gases and acid base status. It is mandatory that the results of these analyses have been obtained before the patients is transferred from the ER for further diagnostic procedures or moved to an in hospital unit. Blood tests for haematological disorders, other electrolyte disturbances and liver and renal function are usually secured in the ER.

Blood lactate, C reactive protein (CRP), carbon monoxide and serum osmolarity are optional and analysed as needed. Urine analyses are primarily for toxicological screening and ketone bodies detection.

Elevated serum levels of neuron specific enolase (NSE) and S-100 after post anoxic brain injury may add prognostic value (49).

1.4.3.2 Lumbar puncture
Examination of cerebrospinal fluid (CSF) plays a central role in diagnosing neurological diseases, especially intracerebral infections and subarachnoidal haemorrhage. A lumbar puncture with measurement of CSF pressure should be performed whenever such conditions are suspected.

1.4.3.3 Radiological and physiological examination
Computed tomography (CT) scanning of the brain has become ubiquitous during the last decades. It is essential in patients with focal neurological findings, when subarachnoidal haemorrhage is suspected and also when the underlying reason for the altered mental state is unclear after a preliminary work up (46). If a lumbar puncture is indicated in patients with clinical suspicion of a space occupying lesion in the posterior fossa, a CT should be performed before the spinal tap (50).

Magnetic Resonance Imaging (MRI) is less available compared to CT. Furthermore, it takes longer time to perform and it is necessary that patients are immobilised to get good quality of the images.

Electroencephalogram (EEG) is useful as an objective test of cortical function in patients who do not respond to normal stimuli. The EEG is very helpful in diagnosing non-convulsive status epilepticus (51-53).

1.5 ETIOLOGIES OF COMPROMISED CONSCIOUSNESS

In the ER patient, impaired consciousness may be of either traumatic or non-traumatic origin. In this thesis, only the non-traumatic causes of compromised consciousness will be discussed in detail.

Non-traumatic coma is usually categorized to be of either structural or metabolic origin. The former is also called focal because there are focal lesions that lead to unilateral findings such as differences in pupil size and reaction to light or palsy in one side of the body. In metabolic conditions leading to impaired consciousness, hemisymptoms are infrequent because there is a more diffuse pathology in the brain. However, in special circumstances discussed below, metabolic disturbances also may lead to focal signs.

1.5.1 Focal origin of unconsciousness

Focal brain lesions that cause unconsciousness by direct effects on the ARAS comprise stroke of ischemic or hemorrhagic origin, intracranial tumour or infections (5, 7, 46). When the focal lesion is located outside the ARAS, indirect effects by movement of brain structures may compromise components of the ARAS, so called brain stem herniation (5, 45, 54-56). Focal lesions are categorized to be of either supra or infratentorial origin. Supratentorial lesions, when responsible for comatose states, compromise the diencephalons, whereas infratentorial lesions affect the upper part of the brainstem.

1.5.1.1 Haemorrhagic stroke

Epidural and acute subdural haematomas are usually of traumatic origin and will therefore not be discussed in detail. However, chronic subdural haematoma often occurs in elderly patients with comorbidities. The pathogeneses is not completely understood. Initially, there is a small bleeding, often but not necessarily following minor trauma. The volume of the haematoma increases over time and leads to symptoms such as headache and fluctuating level of consciousness The diagnosis is made by CT and treatment depends on the clinical symptoms and is either conservative with observation, medical or surgical (5, 57, 58).

Intracerebral haemorrhage may follow rupture of cerebral arteries, arteriovenous malformations, aneurysms, trauma, angiopathy, or bleeding from a tumour (5, 59). The signs and symptoms are more dependent of the location and volume of the haemorrhage than of the etiology. The diagnosis is made by CT and treatment depends on symptoms, location of the haematoma and etiology.

1.5.1.2 Ischemic stroke

Unilateral ischemic stroke in the diencephalon rarely results in impaired consciousness . However, if a cerebral edema develops and progresses, brainstem herniation and coma may follow(5, 56, 60). Thrombosis of the venous sinuses, resulting in an increase in intracranial pressure (ICP), may also lead to impaired consciousness by the same mechanism. Occlusion of the basilar artery leads to ischemia in the medial caudal parts of the hemispheres and may cause coma. Imaging modalities such as CT or magnet resonance imaging (MRI) are diagnostic. In some cases, treatment with thrombolytic agents or thrombectomy may be possible (61).

1.5.1.3 Intracranial infection

Infections may lead to meningitis when microorganisms are transported intracranially by the bloodstream. In some situations, infections in adjacent structures such as sinusitis, otitis and cellulitis may spread intracranially. The inflammatory reaction due to infection can cause both focal and diffuse lesions and therefore different symptoms. The metabolic disturbances and reduced pH promote vasodilatation which will increase CBF and increase ICP. In one third of the patients, focal signs are present and may result from ischemia or compression of underlying cranial nerves passing the subarachnoidal space. Clinical suspicion of meningitis is raised by the presence of the classical triad of fever, nuchal rigidity and alteration of mental status. Diagnosis is confirmed by lumbar puncture and laboratory analysis (62-64). In one third of the patients, focal signs are present (63). The treatment of bacterial meningitis is prompt administration of antibiotics.

Encephalitis is an intracerebral infection most often caused by viruses. Encephalitis caused by Herpes virus is a severe form in which prompt antiviral treatment is imperative for the outcome (65, 66).

1.5.1.4 Tumours

Both primary and metastatic tumours may compromise consciousness by infiltration of the diencephalon or by herniation. Symptoms are often seizures and focal signs of cerebral dysfunction. Diagnosis is primarily made by CT. Treatment depends on etiology, localisation and symptoms and may consist of surgery, stereotactic radiosurgery or chemotherapy (5, 67).

1.5.2 Metabolic origin of unconsciousness

In metabolically caused unconsciousness, there are no intracranial focal lesions causing compression of important structures in the brainstem. Instead, there is a diffuse effect on the cells and receptors in the area that is important for arousal. Sometimes, for example in severe acute hyponatremia or in post cardiac arrest, swelling of brain tissue causes an increase in ICP with concomitant herniation (5, 45, 46).

There is a broad spectrum of disturbances that can be classified as metabolic and may cause unconsciousness by the mechanisms described. The treatment is usually supportive and directed against the underlying illness.

In the following paragraphs, a selection of conditions associated with metabolically mediated loss of consciousness is discussed.

1.5.2.1 Intoxications

A huge amount of different drugs induce unconsciousness when taken in overdose. Sedative-hypnotic drugs are often combined with ethanol (68). Opiates, antidepressants, antihistamines, antiepileptics and psychotropic drugs induce impaired consciousness when overdosed (69). Intake of toxic alcohols such as methanol or ethylene glycol (70) as well as exposure to toxic gases, for example carbon monoxide (71), may give rise to pronounced CNS depression.

Suicidal self-poisoning, accidental overdose, and drug addiction are common causes of intoxications. Certain drugs can be screened for in the ER and the intake of others be suspected from clinical observations, ECG findings, neurological signs and laboratory tests. The clinical picture may be quite variable depending on the drug or drugs ingested. Treatment is related to the suspected drug and the clinical picture and may include gastrointestinal decontamination, administration of an antidote, enhanced drug elimination, and/or symptomatic therapy.

1.5.2.2 Epilepsy

Seizures are characterized by intense, repetitive neuronal discharge followed by postictal metabolic cerebral depression that may vary in severity and duration. The seizure activity increases metabolic demands and CBF. With long standing seizures, there is a risk of depletion of substrate and possible of hypoxic-ischemic neuronal damage. A postictal state may last for several hours (5). Nonconvulsive status epilepticus is a cause of a sustained comatose state, especially in elderly people, or in subjects with accompanying metabolic illnesses that per se can cause unconsciousness (72) .

1.5.2.3 Electrolyte and acid base disturbances

With an acute and marked decrease in serum sodium concentration, as in cases of water intoxication, brain edema follows as a result of osmotic swelling of the brain cells (73). If not promptly recognised and treated, brainstem herniation and death may ensue. In chronic hyponatremic states, compensatory mechanisms reduce the edema formation and clinical symptoms are less pronounced. A too rapid correction of chronic hyponatremia may lead to osmotic injury to the pontine and extrapontine area with permanent impairment of mental status as a consequence (74).

Hypernatremia causes opposite osmotic effects on the brain. Shrinking of brain cells may lead to intracerebral and subarachnoidal bleeding and cause permanent CNS dysfunction (75).

In hypercalcemia, the cause of cerebral dysfunction is poorly understood. An alteration in nervous cell membrane function, mediated by ion channel dysfunction secondary to an increase in extracellular calcium concentration is a likely mechanism. Severe symptoms, like stupor and coma, are more likely to occur with marked hypercalcemia, especially in elderly subjects and in cases where calcium levels have increased rapidly (5, 76).

Several disease states that cause metabolic coma may also cause acid base disturbances. Metabolic acidosis in itself, even when severe, does not cause unconsciousness whereas respiratory acidosis with increased PCO_2 acts as a direct cause of unconsciousness. The diagnosis is established by arterial blood gas analysis.

1.5.2.4 Cardiovascular insufficiency

A marked reduction in cardiac output for any reason may lead to an insufficient CBF and render the patient comatose. Elderly people with cerebrovascular disease and hypertension are more sensitive to reduced blood pressure.

Cardiac arrest leads to unconsciousness within seconds. The recovery from the anoxic episode is related to the time to bystander resuscitation, time to return of spontaneous circulation and the post cardiac arrest care and existing comorbidities (77-79).

1.5.2.5 Respiratory insufficiency

Respiratory insufficiency may lead to reduced level of consciousness either by a reduction in alveolar ventilation and ensuing hypercarbia or by severe hypoxemia, usually as a consequence of a mismatch of ventilation to perfusion (35, 80). The treatment is directed against the underlying disorder and aims at restoring ventilation and oxygenation.

1.5.2.6 Hepatic failure

In acute liver encephalopathy there is an increased permeability of the blood-brain barrier. The mechanism unclear but high levels of ammonia may be a part (81-83).

1.5.2.7 Renal Failure

The mechanism of brain dysfunction in uremia is not clarified but there are correlations with biochemical changes (84).

1.5.2.8 Hypo or hyperglycemia

Glucose is the major energy substrate for the brain. In hypoglycemic coma, too high doses of insulin or oral antidiabetic drugs is usually the underlying cause (85). Alcohol intake, either alone or in combination with insulin or oral antidiabetic drugs, may cause hypoglycemia (85, 86). Rarely, an insulin producing tumour is the cause. The symptoms may vary from mild confusion to deep coma with diffuse and also focal neurological signs and seizures (87). Diagnosis is made by blood glucose testing and the treatment is to restore normal blood glucose levels. Today, the incidence of hypoglycaemic coma in the ER has declined because of more developed prehospital organization (85, 88).

Hyperglycemia per se may cause impaired brain function and lead to coma in two situations, either in diabetic ketoacidosis or in a non-ketotic hyperosmolar state, predominantly in elderly patients (89). Hyperglycemia is treated with insulin and rehydration.

1.5.2.9 Alterations in body temperature

Both hypothermia and hyperthermia may alter consciousness. The temperature of the brain is dependent on the body temperature and also on the metabolism in the brain. Intracerebral temperatures above 41 °C will damage brain cells and areas with pre-existing damage (ie stroke) are more sensitive to hyperthermia .

Apart from external cooling in accidental hypothermia, a decreased body temperature may accompany a variety of illnesses including disorders of the hypothalamus, metabolic disorders such as hypoglycemia and myxedema and is also seen in intoxications with sedative and hypnotic drugs and alcohol. Body temperatures above 32 °C do not cause a reduced level of consciousness. At temperatures below 32 °C, the patients become unconscious with slow respiration and bradycardia. Below 28 °C respiration may cease, pupils become nonreactive and the EEG isoelectric. Hypothermia is treated with rewarming by different techniques depending on the clinical status and also of availability (90).

Hyperthermia of 42 °C or higher may cause unconsciousness (91). In the absence of cerebral injury, fever due to illnesses seldom reaches temperatures above 41 °C. Unconsciousness caused by fever is therefore usually related to the underlying disorder. Heatstroke primarily affects young, not acclimatized, people exercising in hot climate but elderly subjects may display a increased tendency to cerebral dysfunction from elevated body temperature. Three syndromes, malignant hyperthermia, neuroleptic malignant syndrome and serotonin syndrome cause severe hyperthermia and are medical emergencies that require prompt treatment (92).

1.5.2.10 Infections outside the CNS

Systemic severe septic states or septic shock with hypotension and reduced CBF may lead to unconsciousness. This is especially true in older patients with comorbidities (93). A reduced CBF in combination with metabolic reactions leading to increased levels of inflammatory mediators might lead to confusion and in severe cases to unconsciousness.

1.5.2.11 Endocrine emergencies (5, 94)

Adrenal disorders may influence consciousness in a not fully understood manner. Hormones produced in the adrenal cortex have profound effects on the brain. Both insufficient production

(Addison's disease) and increased levels of corticosteroids (Cushing's syndrome) can lead to behaviour changes and loss of consciousness (95). Diagnosis is made by measurements of corticosteroid hormone levels in the blood.

Thyroid disorders may lead to comatose states. Hypothyroidism causes a decrease in CBF and a decrease in glucose metabolism. Patients with myxedemic coma are characteristically hypothermic, hypoventilating and display a slow EEG pattern (96, 97). Diagnosis is made by measurement of thyroid hormone levels in the blood. Hyperthyroidism rarely leads to unconsciousness.

1.5.2.12 Psychogenic coma

Unconsciousness of psychogenic nature is not uncommon, but the topic falls outside of the scope of this presentation and is therefore not discussed further.

2 AIMS

2.1 OVERALL AIMS

The overall aims of this study were to improve the knowledge of common underlying etiologies to coma and of their prognosis, and to find clinical tools to facilitate differential diagnosis of patients with impaired consciousness.

2.2 SPECIFIC AIMS FOR THE RESPECTIVE PAPERS:

Paper I. To investigate the frequency, characteristics and prognosis of different coma etiologies with special focus on poisoning.

Paper II. To investigate the acute and long term prognosis after an episode of non-traumatic coma.

Paper III. To investigate if some routinely recorded clinical features may help to distinguish between focal and metabolic coma.

Paper IV. To investigate the hospital mortality rate among poisoned patients with a pronounced CNS depression on admission.

3 MATERIALS AND METHODS

3.1 STUDY POPULATIONS

This thesis is based on two case series. The main study population consisted of prospectively included adult patients with impaired consciousness (Glasgow Coma Scale Score ≤10) admitted to the ER at Karolinska Universitetssjukhuset, Solna or Södersjukhuset, Stockholm, Sweden during February 2003 to May 2005. The second cohort consisted of all consecutive poisonings admitted to Södersjukhuset from January 2009 to January 2011, retrospectively reviewed (Figure 3).

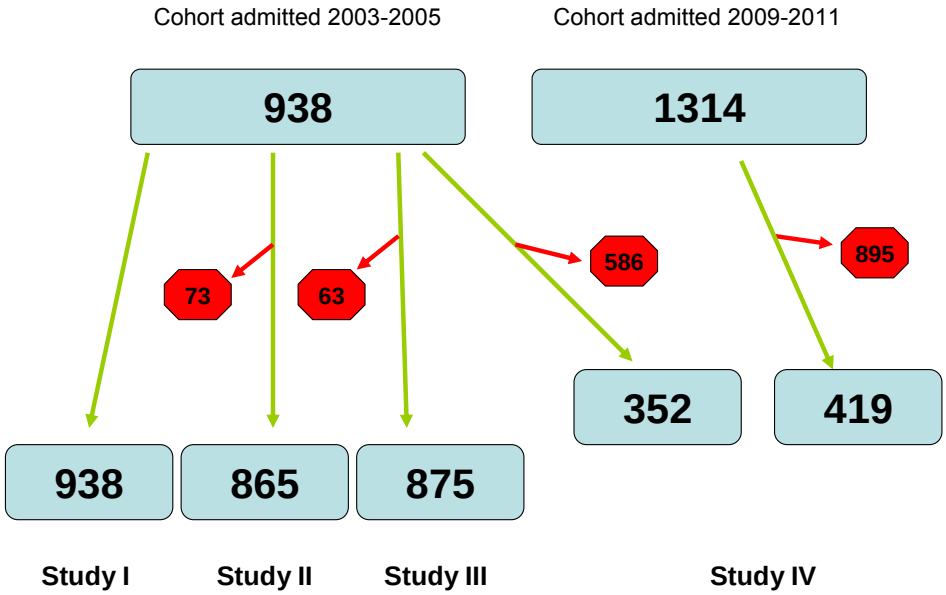


Figure 3. *The upper section shows the main study populations of the studies. The red boxes show the number of excluded patients, see text below. The lower section shows the final study populations investigated in the different papers.*

3.2 METHODS PAPER I-IV PAPER I

Paper I

On admission, the GCS score was entered into a study protocol by specially trained nurses. This pre-study structured protocol was complemented with pertinent data from the medical record within one month from each admission by one of the authors. All available clinical and laboratory data, as well as history information recorded at any time of the clinical course and autopsy information in several instances, were used to ascertain the cause of the impaired consciousness on admission. The definition used to classify a certain patient as a poisoning was as follows. Clear evidence, from the history, laboratory or clinical findings of exposure to a toxic substance including ethanol that could explain the reduced level of consciousness at the time of inclusion should be at hand. If a case of poisoning had an additional possible cause of coma, the patient was still categorized to the poisoning group. Neurological sequelae were retrospectively defined as an impairment of functioning corresponding to a cerebral performance category (CPC) of 2-4 on the 5-graded Glasgow-Pittsburgh Outcome Scale at discharge from hospital.

Paper II
The total patient population enrolled in paper II is identical to that in paper I. In this study the coma etiologies were classified into eight categories as follows: poisoning, epilepsy (status epilepticus, seizures, and/or postictal state), stroke (intracranial hemorrhage or infarction), circulatory failure (post cardiac arrest and/or circulatory shock), infection (meningitis, encephalitis, and/or sepsis), metabolic disorder (hypo/hyperglycemia, hyponatremia, hypothermia, or hepatic failure), malignancy (intracranial tumor), and respiratory insufficiency. Ten patients displayed clinical indications of more than one condition that might have explained the reduced level of consciousness on admission. In these cases we chose the most plausible single reason for the coma. The patients who survived the hospital period were followed up regarding survival for two years after discharge from hospital. If a patient had died, the cause of death was found either in the medical record or through the records of the National Swedish Board of Health and Welfare. In a few cases also international contacts with corresponding authorities were necessary.

Paper III
The total patient population enrolled in paper III is identical to that of paper I and II. The different coma etiologies were here classified into two main groups, metabolic or focal coma, as described by Plum and Posner (5). Available CT scan results were reevaluated in a blinded fashion by a consultant neuroradiologist. Coma etiologies classified into the focal group were cerebral infarction, intracranial hemorrhage, intracranial tumor, and intracranial infection (meningitis or encephalitis). The remaining occurring coma etiologies were accordingly classified into the metabolic group and constituted poisoning, epilepsy (status epilepticus, seizures, or postictal state), circulatory failure (post cardiac arrest or circulatory shock), metabolic disorder (hypo/hyperglycemia, hyponatremia, hypothermia, or hepatic failure), extracranial infection, and respiratory insufficiency. A positive focal neurological sign in the ER was deemed present when: 1. The responsible emergency physician on duty had made a written note in the medical record concerning the findings of a neurological examination, and 2. The pupils of the patient were of different size without any obvious explanation, or the Babinski's reflex was present on one or both sides, or there was a clear asymmetry regarding motor responses to painful stimulation or responses to examination of tendon reflexes.

Paper IV
The paper IV is based on two case series.

Part 1:
Part 1 consists of a series of prospectively included cases of poisoned patients with impaired consciousness at presentation. The population is a part of the cohort described in papers I-III.

Part 2:
Part 2 is a retrospective review of the medical records of all cases of poisoning admitted to the emergency department of South Hospital in Stockholm from January 2009 to January 2011. Pertinent data including GCS score on admission, type of poisoning, and outcome was recorded in a study protocol.

3.3 STATISTICAL ANALYSIS

Paper I.
Planned comparisons were made to evaluate the occurrence of statistically significant interactions between age and underlying cause (poisoning vs. non-poisoning). To evaluate the

effect of age (<40, 40-60, >60 years) on the probability of poisoning, binary logistic regression was performed.

The probability of poisoning was expressed as log (odds) in the model and the results are presented as odds ratio (OR) with 95% confidence intervals (CI) and p values. To determine whether any age classes differed statistically in odds, post-hoc tests were carried out. A two-sample t-test for independent groups, assuming equal variances in each group, was performed to assess the mean differences between groups. Proportions were compared using the Chi-square test.

Paper II.
For all hospital survivors Cox's regression analysis was used to evaluate the influence of the different coma etiology categories on the 2-year follow-up mortality. Hazard ratios (HR) with 95% confidence intervals [CI] between the different categories were adjusted for age and gender inequalities. Kaplan-Meier curves were used to illustrate the mortality during the 2-year follow-up. The study population was also divided into two groups depending on the degree of consciousness on admission: one group with a GCS score of 3-6 on admission and one with a GCS score of 7-10. Cox's regression analysis was again used to compare the mortality rates of these two groups.

Paper III.
Univariate and multiple logistic regression analyses were performed to find important relationships between clinical variables (e.g. age, blood pressure, body temperature) and their relation to the binary outcome (the two main coma etiologies). The results of these findings were reported by means of odds ratios (OR) and their corresponding 95% confidence intervals (CI). Hosmer-Lemeshow test and ROC curve (Receiver operating characteristics) were used to determine goodness of fit for the model. When important variables where identified and adjusted for, the next step was to find a clinically applicable and powerful model for predictions to use as a tool in the ED (i.e. a model that is powerful enough by means of clinical expertise, predictions accuracy and goodness of fit statistics). The continuous variables in the model were categorized (e.g. systolic blood pressure >150 mmHg and age >50 years) for simpler classification.

Paper IV.
Differences in mortality rates were tested by Fischer's exact test.

Analyses were performed with SAS 9.2 (SAS Institute Inc. Cary), and by *STATISTICA* 8.0 and 10.0 (StatSoft Inc. Tulsa). *P* values less than 0.05 were considered to indicate statistical significance.

4 RESULTS

This thesis is mainly based upon the results from the cohort that was prospectively included at two major teaching hospitals in Stockholm during the years 2003-2005. The data were retrospectively collected from the medical records within one month from each admission. This study design implies that some of the variables investigated were missing in some of the patients. Table 3 gives a summary of this circumstance.

Table 3 *shows a summary of clinical findings in the emergency room among the 938 unresponsive patients who constituted the main study population of this thesis.*

Variables	Clinical findings Number / value	Number of the variable noted in the medical records (%)
Patients	N=938	938 (100)
Mean age (range)	59 years (15-98)	938 (100)
Gender, male	N=353 (52%)	938 (100)
GCS score, mean	6 (SD:2.4)	938 (100)
Systolic blood pressure, mean	136 mmHg (SD: 41)	916 (98)
Heart rate, mean	93/min (SD:27)	896 (96)
Respiratory rate, mean	19/min (SD:13)	308 (33)
Temperature °C, mean	36.7 (SD:1.8)	588 (63)
Temperature <32 °C	N=10 (1.7%)	10/588
Temperature >39 °C	N=5 (0.9%)	5/588
Clinical signs of focal pathology	N=287	627 (67)
Glucose mmol/l, mean	8.9 (SD 7.7)	770 (82)
Glucose < 6.0 mmol/l	N=236 (31%)	236/770
Glucose < 2.5 mmol/l	N=16 (2.1%)	16/770
pH mean	7.29 (SD 0.17)	282 (30)
pH <7.1	N=32 (11%)	32/282
pH >7.5	N=8 (2.8%)	8/282
PCO_2 kPa, mean	6.8 (SD:3.1)	278 (30)
PCO_2 >7.0 kPa	N=71 (26%)	71/278
Sodium mmol/l, mean	139 (SD:6.3)	841 (90)
Sodium >155	N=8 (1.0%)	8/841
Sodium <125	N=18 (2.1%)	18/841
Potassium mean	4.0 (SD:0.7)	791 (84)
Potassium >7 mmol/l	N=5 (0.6%)	5/791
Potassium <3 mmol/l	N=20 (2.5%)	20/791
Prehospital orotracheally intubated	N=40 (4.3%)	40/938
Acutely performed CT scan	N=409 (44%)	409/938

SD, standard deviation; CT scan, computer tomography scanning; GCS, Glasgow coma scale.

Paper I

During the study period 938 patients were enrolled, 509 at the Karolinska University Hospital Solna and 429 at the South Hospital. Their mean age was 59 years (15-98) and 447 (48%) were women. Poisoning had caused the unconsciousness in 352 cases (38%). In the remaining 586 cases (non-poisoning group) the underlying cause of the impaired consciousness was a focal neurological lesion (i.e. stroke or brain tumor) in 225 cases (24%), a metabolic disturbance or diffuse neurological lesion in 196 (21%), epileptogenic (seizures, postictal state) in 116 (12%), and psychogenic in 8 (1%), and was still not clarified at hospital discharge or after death in 41 cases (4%).

The mean age in the poisoning group was 43 years, compared to 69 years in the non-poisoning group ($p < 0.001$). In patients below the age of 40 years (n=206) the impaired consciousness was due to poisoning in eight out of ten, whereas in those older than 60 years (n=458) nine out of ten had some other underlying cause (OR 33, CI 21-51, $p < 0.001$) (Fig 4).

The mean GCS score on admission was 6 both in the poisoning and in the non-poisoning group. The duration of coma was significantly shorter among the poisoned patients (13 vs 50 hours, $p < 0.001$, median 5 vs 12 hours). Ninety-five percent of the patients in the poisoning group were discharged alive and without neurological sequelae, compared to 43% of the patients in the non-poisoning group ($p < 0.001$) (Table 4).

Table 4. *Age, level and duration of unconsciousness, number of cases with neurological sequelae and hospital mortality in the two study groups.*

	Non-poisoning (n=586)	Poisoning (n=352)
Mean age, years	69	43
Mean GCS score on admission	6	6
Unresponsive more than 12 hours	279 patients (48%)	62 patients (18%)
Sequelae at discharge	104 patients (18%)	7 patients (2%)
Fatal outcome	227 patients (39%)	10 patients (2.8%)

Thirteen patients in the poisoning group (4%) underwent gastric lavage and 28 (8%) received activated charcoal. Naloxone was given to 85 patients with poisoning (24%), of whom 39 responded. Flumazenil was administered to 136 patients with poisoning (39%), of whom 79 responded. There was no severe complication related to the administration of either of these two antidotes. Complications in terms of seizures and respiratory insufficiency were less common among the poisoned patients but intensive care admittance did not differ significantly. The number of patients where coma etiology could be established before discharge from the ER was significantly higher among poisonings. Of the 352 patients with poisoning, 27 (8%) had at least one episode of seizures, 37 (11%) received mechanical ventilation, and 104 (30%) were admitted to an ICU (Figure 5).

In ten of the 352 cases of poisoning, there was one distinct additional explanation for the unconsciousness on admission over and above the intoxication, namely traumatic subdural hematoma (3 cases), hypothermia (2), near-drowning/hypothermia (1), cerebral infarction (1), subarachnoid hemorrhage (1), intracerebral bleeding (1), or hypoglycemia (1 case).

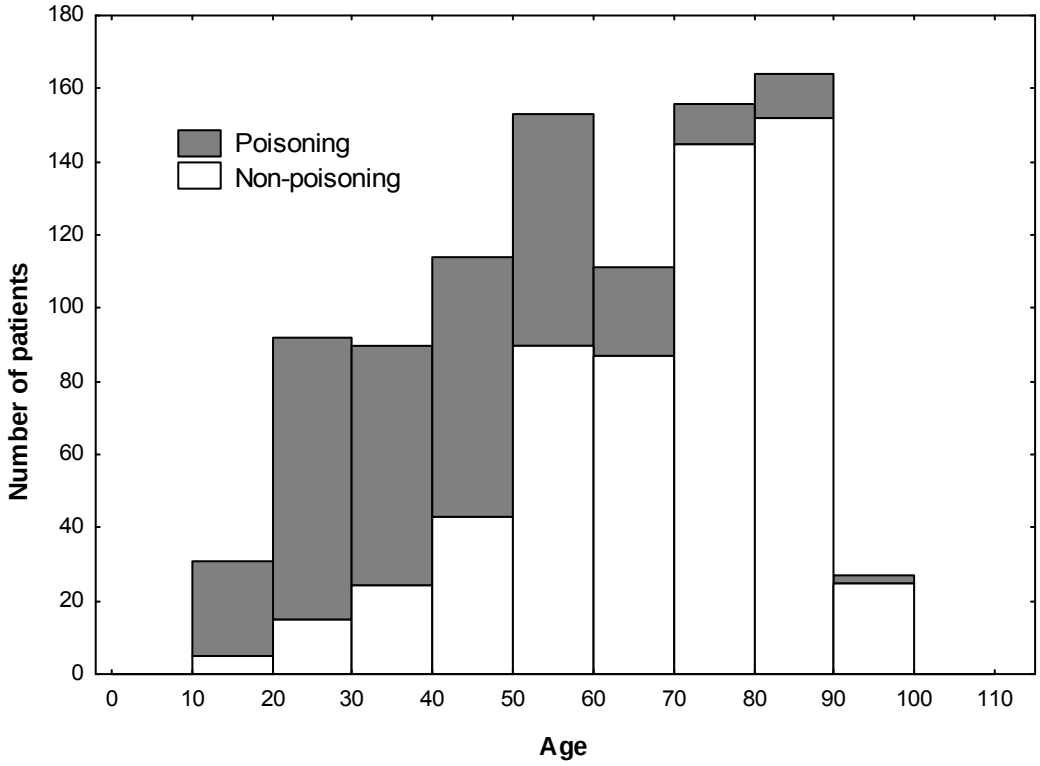


Figure 4. *The relation between age and diagnoses. Dark is poisoning and white non-poisoning.*

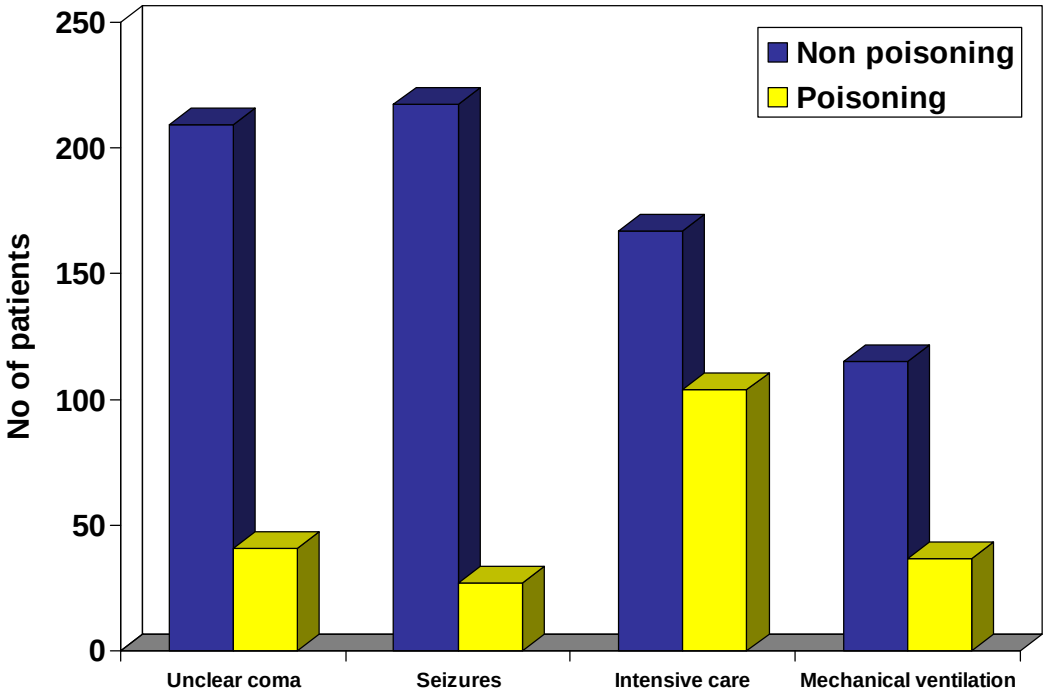


Figure 5. *Number of patients with unclear coma, seizures, intensive care treatment and mechanical ventilation in the different groups. Non-poisonings in blue bars and poisonings in yellow.*

Paper II

A total of 938 patients were enrolled during the inclusion period. Seventy-three patients (7.8%) were excluded for the following reasons: 40 because their coma etiology was still not clear at hospital discharge, 25 due to unknown identity and eight because their unconsciousness was shown to have been of a psychogenic nature. The remaining 865 patients had a mean age of 59 years (15-98) and 52.6 % were male. Poisoning, stroke, and epilepsy were the most common causes of unconsciousness on admission. The mean hospital stay varied between the different coma etiology categories, from 2 days for the patients with poisoning to 12 days for the infection category. The total hospital mortality rate among the 865 patients was 26.5% (229 deaths). Table 5 presents the age and gender distribution, the hospital mortality rate, and the total accumulated long-term mortality of the patients in the eight coma etiology categories. The table also includes the expected age-matched 1-year mortality in the Swedish population (98). The total accumulated mortality for the whole study population after 2 years of follow-up was 43.0 % (372 deaths). When the two coma etiologies with the most favourable prognoses were excluded (poisoning and epilepsy), the remaining cohort of 423 patients had a hospital mortality of 52%, an accumulated 1-year mortality of 67%, and a total 2-year mortality of 71% (Table 5).

As the total hospital mortality was 26.5%, 636 patients were discharged alive from hospital. The 2-year prognosis in this group is illustrated in Figure 6. Although the number of patients in all coma etiology categories except poisoning, epilepsy, and stroke was rather low, statistically significant differences were found in a majority of the inter-category comparisons. There were clear differences between the malignancy category and all other coma etiologies, with a hazard ratio (HR) ranging from 5.1 [95% confidence interval 2.0-12.7] when compared with the circulatory category to HR 12.7 [6.0-26.8] when compared with epilepsy. The patients in the circulatory category were at a higher risk, with HR above 2, when compared with patients in the epilepsy, poisoning, or stroke category. Patients with metabolic or infectious reasons for the unconsciousness were at higher risk compared with epilepsy, HR 2.1 [1.1-4.4] and 2.1 [1.1-3.9], respectively, and compared with poisoning, HR 1.8 [0.9-3.6] and 1.8 [1.0-3.3], respectively. In comparisons of poisoning versus epilepsy, poisoning vs stroke, epilepsy vs stroke, metabolic vs infection, and metabolic vs circulatory as etiologic categories, HR was low, and in the rest of the inter-category comparisons HR was on an intermediate level, ranging from 1.2 to 1.7.

In addition to the coma etiology, the level of consciousness on admission was also important for the prognosis. Patients with a GCS score of 3-6 (n=496; mean age 59.4 years) had a significantly higher hospital mortality rate, 32.9%, than those with a GCS score of 7-10 (n=369; mean age 59.2 years), 17.9%, HR 1.6 [1.3-2.0], P <0.001. However, the level of consciousness on admission did not significantly influence the long-term prognosis in the hospital survivors.

Table 5. *Acute and total accumulated long-term mortality rates for the whole study population and for the eight different coma etiologies.*

Coma etiologies	Number (%)	Proportion male %	Mean age years	Hospital mortality %	Total 1-year mort. %	Total 2-y mort. %	Age-matched 1-y mortality in the Swedish population
Poisoning	329 (38.0)	55.6	44	2.4	10.9	13.7	0.11%
Stroke	213 (24.6)	43.7	74	60.6	70.9	73.7	2.2%
Epilepsy	113 (13.1)	55.8	61	0.9	15.9	23.9	0.8%
Circulatory	60 (6.9)	65	71	71.7	85.0	86.7	2.2%
Infection	56 (6.5)	62.5	68	26.6	51.8	60.1	1.3%
Metabolic	44 (5.1)	40.1	57	15.9	31.8	40.9	0.5%
Respiratory	33 (3.8)	45.5	78	60.6	72.7	75.8	3.7%
Malignancy	17 (2.0)	52.9	65	29.4	76.5	88.2	1.3%
Study population	865 (100)	52.6	59	26.5	38.9	43.0	0.5%

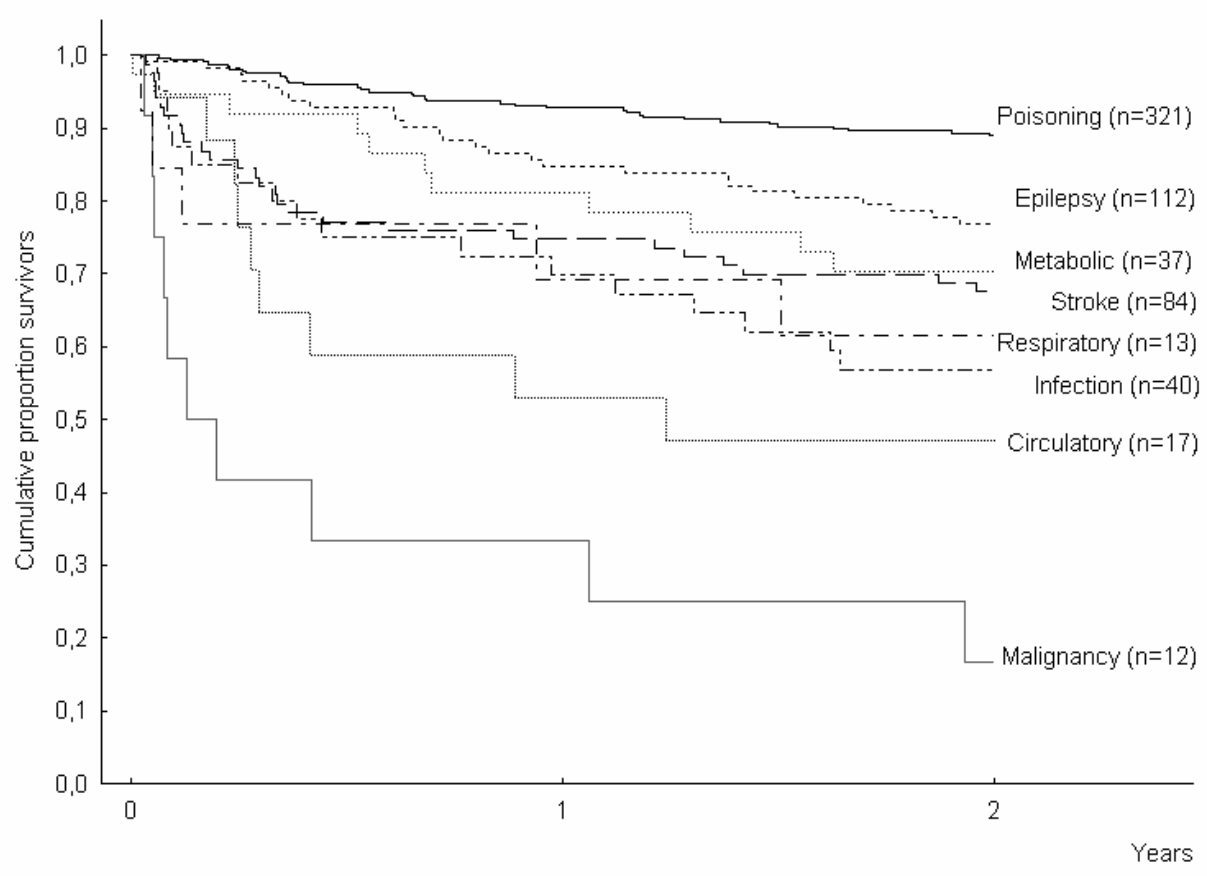


Figure 6. *Kaplan-Meier curve illustrating the decreasing number of survivors in the different coma etiologic categories during the 2-year follow-up among the 636 patients who were discharged alive from hospital. The number of hospital survivors in each category is indicated.*

Paper III

A total of 938 patients were enrolled during the inclusion period. Sixty-three patients (6.7%) were excluded for the following reasons: forty-one because their coma etiology was still not clear at hospital discharge, 14 because they had more than one explanation to the coma and 8 because their unconsciousness was shown to have been of a psychogenic nature. The remaining 875 patients had a mean age of 59 years (15-98) and 464 (53%) were male. Among this final study population, 633 patients (72.3%) were classified into the metabolic coma group and 242 (27.7%) into the focal group. The most common causes of unconsciousness in the metabolic group were poisoning and epilepsy, whereas stroke (cerebral infarction or intracranial hemorrhage) constituted the most frequent coma etiology in the focal group (Table 6).

Table 7 presents a comparison of age and gender distribution, clinical features in the ER, acutely performed interventions, frequency of intensive care treatment during the hospital course, and outcome between patients with a metabolic or a focal underlying coma etiology. There was no difference in the frequency of intensive care treatment between the groups. An acute CT scan was performed in 24% of the patients who were later shown to have a metabolic disturbance compared to 90% of the patients in the focal coma group. In the metabolic group, 7 (5%) of the performed CT scans showed pathological findings, four of which were evaluated as unclear smaller changes without clinical significance, two as acute global ischemia due to non-focal disorders and one as multiple old infarctions. In the focal group, 182 (84%) of the performed CT scans showed pathological findings. The patients with a focal origin of the coma had a much higher hospital mortality rate, 56% (n=135) versus 14% (n=89).

Gender and age were known in all patients already in the ER. The blood pressure on admission was not noted in the medical record in 22 patients (2.5%). A written statement in the medical record concerning result of a neurological examination in the ER was missing in a part of the study population. In the metabolic coma group observations regarding presence of focal neurological signs were noted for 358 patients (57%), whereas 223 such notes where made in the focal group (92%). Eighty-eight patients in the metabolic group showed at least one positive focal sign (25%). The dominant underlying coma etiology among these 88 patients was epilepsy, n=50 (57%), followed by poisoning, n=13 (15%). The other metabolic diagnoses were evenly distributed among the remaining 25 patients. In the focal group, 178 patients (80%) displayed at least one positive focal sign in the ER (Table 7).

Among all the clinical variables that were recorded in the ER, the following were statistically investigated regarding their prediction of a metabolic or focal underlying condition (odds ratios, expressed as crude numbers, and their 95% confidence intervals): age, gender, GCS score, result of neurological examination, blood pressure, heart rate, respiratory rate, body temperature, pH, PaO_2, $PaCO_2$, serum potassium, serum sodium, serum glucose and serum creatinine. Age, gender, blood pressure and result of neurological examination were found to be significantly different between patients in the metabolic group and those in the focal coma group. After adjusting for pertinent variables as age and blood pressure, and categorization for age and blood pressure (i.e. systolic blood pressure >150 mmHg and age >50 years), multiple logistic regression analyses were performed. The following parameters were found significant: age, blood pressure, focal neurological signs and gender (Table 8).

In order to find a predictive and clinically useful combination of parameters, probability tests were performed. The combined findings for age, blood pressure and result of neurological examination were shown to be highly predictive of either a metabolic or a focal coma. In this final predictive model, 569 out of the total 875 patients fulfilled the three variables included, i.e.

a written statement regarding result of a neurological examination in the ER was noted in the medical record as was the blood pressure on admission and the age of the patient. Gender as a variable did not add anything to this statistic model and was therefore excluded. The probability for a patient with the combination of age ≤50 years, systolic blood pressure ≤150mmHg and negative focal neurological signs of having a metabolic coma was 96.1%. The probability for a patient with the combination age >50 years, systolic blood pressure >150mmHg and positive focal signs for having a focal coma was 79.8 % (Table 9).

Table 6. *The study population (n = 875) divided into cases with metabolic or focal coma, and into the different subclasses of coma etiologies (diagnoses).*

Metabolic coma	**n (%) 633 (72.3)**	**Focal coma**	**n (%) 242 (27.7)**
Poisoning	342 (54)	Cerebral infarction	104 (43)
Epilepsy	116 (18.3)	Intracranial hemorrhage	104 (43)
Extracranial infection	39 (6.2)	Intracranial tumor	17 (7)
Cardiac arrest	42 (6.6)	Intracranial infection	17 (7)
Circulatory Shock	17 (2.7)		
Respiratory failure	33 (5.2)		
Hypoglycemia	17 (2.7)		
Hyperglycemia	8 (1.3)		
Hyponatremia	9 (1.4)		
Hepatic failure	8 (1.3)		
Hypothermia	2 (0.3)		

Table 7. *A comparison of clinical features recorded in the emergency department, acutely performed interventions, frequency of intensive care unit treatment and outcome between patients with a metabolic coma and patients with a focal underlying etiology.*

Clinical observations	**Metabolic coma n=633**	**Focal coma n=242**
Age, mean (years)	53.7 (SD: 20.1)	72.5 (SD: 14.8)
Gender, male	353 (55.8%)	110 (45.5%)
Glasgow Coma Scale score, mean	5.9 (SD: 2.4)	6.1 (SD: 2.4)
Systolic blood pressure, mean	126 mmHg (SD: 36)	164 mmHg (SD: 41)
Clinical signs of focal pathology	88/358[*] (24.6%)	178/223[**] (79.8%)
Orotracheally intubated	98 (15.5%)	48 (19.8%)
Acutely performed CT scan	151 (23.9%)	217 (89.7%)
Pathological findings on CT scan	7 (4.6%)	182 (83.9%)
ICU treatment	186 (29.4%)	72 (29.8%)
Hospital mortality	89 (14.1%)	135 (55.8%)

[*)] In 358 of 633 patients, notes regarding focal neurological signs were made in the medical records.
[**)] In 223 of 242 patients, notes regarding focal neurological signs were made in the medical records.
SD = standard deviation; CT scan = computer tomography scanning of the brain; ICU = intensive care unit.

Table 8. *Odds ratios for prediction of a metabolic coma for some clinical features recorded in the emergency department.*

Clinical features	Odds ratio	95% CI
Age ≤50 years	4.0	[2.15-7.33]
Age >50 years	0.25	[0.14-0.46]
Blood pressure, systolic ≤150 mmHg	3.0	[1.96-4.59]
Blood pressure, systolic >150 mmHg	0.33	[0.22-0.51]
Focal sign, negative	8.0	[5.2-12.4]
Focal sign, positive	0.12	[0.08-0.19]
Male gender	1.54	[1.01-2.37]

CI = confidence interval

Table 9. *Prediction of the two main forms of coma, metabolic or focal, based on three clinical features easily recorded in the emergency department. The statistic calculations are based on the 569 patients who had full data recorded in their medical records.*

	Patients ≤50 years and systolic blood pressure ≤150 mmHg and no focal neurological sign	Patients >50 years and systolic blood pressure >150 mmHg and focal neurological sign
Probability for metabolic coma [95% CI]	0.96 [0.80-0.99]	0.20 [0.03-0.67]
Probability for focal coma [95% CI]	0.04 [0.01-0.20]	0.80 [0.33-0.97]

Goodness of fit ascertained with Hosmer-Lemeshow test (P=0.90) and Receiver operating characteristics (ROC) curve with an area under curve of 0.84. Prediction accuracy for metabolic origin was 80.9% and for focal origin 75.2%. CI = confidence interval.

Paper IV

Part 1:

During the study period 938 patients were enrolled. Five hundred and eighty-six were excluded because they were shown to have had another explanation to their unconsciousness than poisoning. The remaining 352 patients constituted the final population. Their mean age was 43 years (range 15-95) and 41.8% were women.

The 352 poisonings had ingested the following toxic agents: ethanol alone in 128 patients (36%); ethanol in combination with mainly sedative-hypnotics in 59 (17%); sedative-hypnotics in 70 (20%); heavy narcotics, mainly heroin, with or without ethanol, in 36 (10%); and miscellaneous toxicants in the remaining 59 cases (17%). The latter group consisted of overdoses of opiates other than heroin (11 cases), tricyclic antidepressants (6), anticholinergics (5), carbon monoxide (4), lithium (2), valproate (2), gamma hydroxybutyrate (2), carisoprodol (2), insulin (1), meprobamate (1), carbamazepine (1), baclofen (1), unknown (4) or mixed unspecified drugs (17 cases).

The hospital mortality rate was 2.8%. Five of the ten fatal cases had a poisoning related to drug and alcohol abuse, three other cases died as a result of severe aspiration, one patient was found unconscious in an apartment all in flames and died from fire smoke inhalation despite prompt treatment with hydroxycobalamine and hyperbaric oxygen. The tenth fatality was due to a

massive amitriptyline poisoning (Table 10). The degree of CNS depression on admission significantly influenced the prognosis. A GCS score of 3-6 (n=198) was associated with a higher hospital mortality rate than a GCS score of 7-10 (n=154) ($p < 0.05$).

Part 2:
A total of 1,314 admissions because of poisoning to the emergency department of South hospital were recorded during the 2-year-period. The overall hospital mortality was 0.8% (10 fatalities) while the subgroup with a GCS score ≤10 (419 patients or 32%) had a mortality of 2.4%. The 419 unresponsive poisonings had ingested the following toxic agents: ethanol alone in 83 patients (20%); ethanol in combination with mainly sedative-hypnotics in 115 (27%); sedative-hypnotics in 67 (16%); heavy narcotics, mainly heroin, with or without ethanol, in 19 (4.6%); and miscellaneous toxicants in the remaining 135 cases (32%).

The mean age of the ten deaths was 43 years and eight were males. Eight of the fatalities had a poisoning related to drug and alcohol abuse and among these, two had overdosed heroin, one methadone, one dextropropoxyphene and ethanol, three had overdosed a mixture of drugs other than heroin including amphetamine, benzodiazepines and technical alcohol, and one had injected a solution of crushed clonazepam tablets. The ninth fatal case was due to a suicidal overdose of mainly digoxin, and the tenth fatality was caused by complications to a large overdose of sertraline. The degree of CNS depression on admission significantly influenced the prognosis also in this case series. A GCS score of 3-6 (n=246) was associated with a higher hospital mortality rate than a GCS score of 7-10 (n=173) ($p < 0.01$). Table 11 shows all patients from both case series with a GCS score ≤10, divided into two groups depending on the degree of CNS depression on admission.

Table 10. *The ten fatal cases of poisoning in the observational study, i.e. part 1 of this report.*

Sex / age	Clinical course
M / 52 years	Heroin abuser. Found cyanotic with apnea. Resuscitated cardiac arrest during transport. Naloxone with minimal effect. S-ethanol 60 mmol/L. Died with anoxic brain damage after 29 days in the intensive care unit (ICU).
F / 38 years	Found outdoors hypothermic (core temp. 20.3° C) with an empty oxazepam can in her pocket and a bottle of alcohol beside her. Warmed up with heart-lung machine. Signs of severe aspiration. Died after two days in the ICU.
M / 81 years	Chronic disease and depression. Found unconscious in bed with signs of severe aspiration. Flumazenil had a clear but short-lived effect. Died from circulatory collapse after 2 days of mechanical ventilation.
M / 53 years	Witnessed intake of large amounts of alcohol. Had suddenly fallen, vomited, and aspirated. Cardiac arrest on arrival of the ambulance. Resuscitated. S-ethanol 84 mmol/L. Repeated cardiac arrests. Died eight hours after ICU admission.
F / 79 years	Parkinson's disease and depression. Found in bed with an empty can of diazepam beside her and with signs of severe aspiration. Flumazenil had a repeatedly clear but short effect. Died after 7 days with severe pneumonia despite antibiotics.
M / 63 years	Chronic alcoholic. Found hypothermic (core temp. 25.2° C). S-ethanol 46 mmol/L. Warmed up conservatively. Mechanical ventilation during one day. Died from circulatory collapse day 7, probably triggered by an alcohol withdrawal syndrome.
F / 38 years	Admitted 2 hours after a massive intake of amitriptyline, propiomazine, and alcohol. Wide QRS complexes. Treated with sodium bicarbonate, gastric lavage, charcoal etc, but died from arrhythmias and seizures five hours after admission.
F / 92 years	Found unconscious in an apartment all in flames by smoke-helmeted firemen. COHb 30% on admission. Superficial burns. Treated with hydroxycobalamine and hyperbaric oxygen, but died after two days.
M / 54 years	Chronic alcoholic. Found with signs of severe head injury. S-ethanol 91 mmol/L. Emergency CT scan of the brain showed multiple contusion hemorrhages and a subdural hematoma. Repeated seizures. Died 42 hours after admission.
M / 40 years	Known mixed drug abuser. Found with ongoing seizures. Maximally dilated pupils. S-ethanol 82 mmol/L. CT scan of the brain showed a large subdural hematoma. Died six hours after admission.

Table 11. *The 771 cases of poisoning with a GCS score ≤10 on admission pooled from both case series of this report, divided into two groups depending on the degree of CNS-depression on admission. GCS = Glasgow coma scale.*

Degree of CNS-depression	Number of patients	Mean age (years)	Mean s-ethanol on admission	Hospital mortality rate
GCS score 3-6	444 (58%)	41.6	58.6 mmol/L (n=265)	4.3% (n=19)
GCS score 7-10	327 (42%)	42.2	52.8 mmol/L (n=196)	0.3% (n=1)

5 DISCUSSION

One of the main findings in this thesis on non-traumatic coma, as described in paper I and II was that being admitted to hospital in an unconscious state is a serious incident irrespective of the origin of unconsciousness.

The one-year mortality rate in our study was 39% overall, ranging from 10.9% (poisoning) and 15.9% (epilepsy) for the most benign causes of unconsciousness to 85% (circulatory) for the most serious cause. Only a few studies have previously been published in this field, and none as large as ours. Levy et al, with 500 patients included, reported 1981 about severe prognosis with a 1-year mortality of 88% in comatose patients, poisonings excluded (12). In our study the overall 1-year mortality was 39% but 56% when poisonings were excluded. However, even if we exclude all patients in the etiologic categories with the best prognoses in our material (poisoning and epilepsy) we still have a 1-year mortality of 67%. Hopefully, this discrepancy to Levy et al. reflects some treatment improvement during the past 30 years. Another explanation for the difference is that we included patients admitted with a GCS score equal or less than 10 whereas Levy et al, included patients with a score of 8 or less.

A second major finding in this thesis was that the coma etiology and the level of consciousness on admission were significant determinants of the prognosis. These results are in accordance with those reported by Sacco et al from 1990 (13).

Another important finding in paper I was that poisoning was found to be the most common underlying cause of impaired consciousness among adult patients admitted to the non-surgical ER. This was noted at both hospitals where recruitment was performed, 352 poisonings among 938 cases (38%). This finding is in accordance with the study of patients with an altered mental status by Kanich et al (11) in which cases of trauma was also included. Among patients below the age of 40, the impaired consciousness was caused by poisoning in no less than 80%. By contrast, in patients over 60, poisoning was the cause in only 11%. This means that young age alone is a very strong predictor of poisoning as an underlying cause of coma. The average GCS score on admission was identical in the poisoning and non-poisoning groups, and consequently the level of consciousness was not useful in distinguishing between poisoning and other underlying causes.

The outcome among the patients with poisoning was favourable compared to that in the non-poisoning group.

The long-term prognosis in patients recently hospitalized because of self-poisoning is known to be worse than that in an age-matched population (99). Nordentoft et al reported a 1-year mortality rate of about 5% and a 2-year rate of almost 10% (100). The corresponding rates in the paper II were 8.7% and 12.5%. These relatively small differences may well be due to the fact that all patients with poisoning in our study were unconscious on admission, probably indicating a serious suicide attempt.

The reported hospital mortality among patients with status epilepticus varies between 7% and 46% (101). In paper II the corresponding rate in the epilepsy group was only 0.9%, most probably due to the fact that only a minority of our patients fulfilled the criterion of status epilepticus. Regarding the long-term prognosis in patients discharged alive after hospitalization for seizures, our results are comparable to the limited reports in the literature. Logroscino et al

reported a 2-year mortality of approximately 20-25% after an episode of status epilepticus (102), which is almost identical to the corresponding rate of 23.2% in our mixted epilepsy population.

The accumulated 1-year mortality among the patients with stroke in the paper II was 70.9%, a figure correlating fairly well to previous reports (103, 104). Among the 60 patients with circulatory shock as the coma etiology in our study, 43 were admitted after cardiac arrest. The accumulated 1-year mortality in this category was 85%, only slightly lower than the corresponding rate of 90% reported by Levy et al some 20 years ago (12). One might have expected a clearer prognostic improvement in these emergency cases in view of the more aggressive therapy approach, including use of the hypothermia concept, in recent years (49, 79).

The 33 patients in the respiratory insufficiency category in our study had a high hospital mortality of 60.6% and an accumulated 2-year mortality of 75.8%. All these patients were over the age of 60 years. Ai-Ping et al reported an accumulated 2-year mortality of 50% among patients with respiratory failure requiring intensive care (105). The discrepancy may be explained by the older age of our patients and the fact that all were unconscious on admission.

Patients with a metabolic disorder as cause of their coma constitute a heterogeneous group who had an intermediate prognosis in our study. The patients with severe infection as coma etiology had a hospital mortality of 26.6% and a serious long-term prognosis. Annane et al concluded that the prognosis in septic patients had improved, but that sepsis still carried mortality rates of approximately 35-70% (106). Flores-Cordero et al reported that the mortality among patients with meningitis presenting with coma was about 33% (64).

The 17 patients in the paper II with an intracranial tumor as the cause of their coma had an intermediate hospital mortality rate of 29.4%, but as expected, a very poor long-term prognosis.

The methods of classifying coma into groups based on related etiologies varies in the literature (7,10,11). The two main groups, metabolic and focal coma, that were used in the paper III mainly follows the classification method of Plum and Posner which, in addition to cerebral infarction, intracranial hemorrhage and intracranial tumour also includes intracranial infections such as encephalitis as focal conditions (5). The rationale for this is partly that all these conditions may warrant an acute CT scan, partly that these coma etiologies have a much poorer prognosis than the coma etiologies in the metabolic group (12,20,46).

It is commonly assumed that almost all patients with a focal coma display pathological focal signs, whereas patients with a metabolic coma do not. In the present study pathological focal signs, i.e. anisocoria, lateralization of motor responses, or the presence of the Babinski's sign, were recorded in 79.8% of the cases with focal coma where neurological examination was documented. The inclusion of the intracranial infections into the focal coma group explains a part of the missing 20%, but also the fact that patients with slowly progressing intracranial diseases or diffuse lesions in the cortex may present unconscious without any sign of focal pathology (5). The corresponding proportion of patients with positive focal signs in the metabolic group was 24.6%. Reasons for this surprisingly high proportion may be that around 10% of a healthy population has an isolated anisocoria and that some of the study patients had neurological sequelae after a previous stroke (47). The most important explanation, however, was probably that notes regarding focal signs where made only in 358 of the 633 patients with metabolic coma, and it is reasonable to assume that a vast majority of the remaining 275 patients did not display any focal neurological sign.

A major finding in paper III was that approximately three quarters of the study population (unselected, non-surgical patients presenting to the ER with impaired consciousness) were suffering from a metabolic, i.e. a non-focal, condition. In a previous study by Levy et al, the corresponding proportion of patients with a metabolic underlying disorder was around two thirds (12). However, in that study poisonings were not included.

The other important finding in the paper III was that three routinely recorded clinical features, namely young age, low or normal blood pressure and absence of focal neurological signs on admission were found to be strongly associated with a metabolic condition. Patients who fulfilled all these three metabolic markers had a statistic probability for having a metabolic coma of 96%. On the other hand, the probability for a patient with the combination age >50 years, systolic blood pressure >150mmHg and positive focal signs for having a focal coma was 80%. The combination of these three clinical features compose a simple decision aid, not described before, which may help emergency physicians to rapidly and more correctly distinguish patients with metabolic conditions from those with a focal coma.

The acute performance of computed tomography of the brain has more or less become routine in cases presenting with coma worldwide. When a focal lesion is suspected and an indication for acute neurosurgical or thrombolytic treatment is reasonable there is no doubt about its indication. However, if the impaired consciousness is due to a metabolic disorder, an emergency CT scan is most often unnecessary, resource demanding and carries a risk of delaying important treatment and ICU-monitoring. In the present observational study, 151 CT scans were acutely performed among the patients in the metabolic group (24%).

The main finding in Paper IV was that the hospital mortality rate among the 419 comatose cases of poisoning in the retrospective case series 2.4%. This is in agreement with the mortality rate of 2.8% in the observational case series (paper I). Heyerdahl et al, reported a similar mortality rate of 3% among comatose poisoned patients in Norway (107). These findings contrast with the previously frequently reported short term mortality rates of around 0,5% in acute poisoning. Thus in the presence of significant CNS-depression on admission the short term prognosis in acute poisoning is considerably worse than previously reported (108-113). Approximately 25-30% of all cases of poisoning admitted to hospital have been reported to present with a pronounced CNS depression (107, 111, 114). In our material this group constituted 32% of all cases of poisoning admitted to hospital.

Another finding in paper IV was that the degree of unconsciousness was important for the prognosis. Nineteen of the 20 fatalities occurred among the 444 patients in the two case series that had a GCS score of 3-6 on admission. The hospital mortality rate among these cases with deep coma was thus 4.3%.

6 CONCLUSION

- Poisonings was the most common cause of unconsciousness in the non-surgical ER and young age was a strong predictor of this condition.
- The acute prognosis in patients presenting with coma to the ER is serious and depends both on the etiology and the depth of coma. Long term prognosis among hospital survivors was not influenced by initial GCS. In general, the prognosis was much more favourable for the coma etiologies poisoning and epilepsy.
- Age, blood pressure and neurological signs were found to be strongly associated with the two main coma categories, metabolic and focal. Young adults admitted to the ER with a low or normal blood pressure and without focal neurological signs most probably suffer from a metabolic disorder, wherefore emergency CT scan normally may be avoided.
- Around one third of hospitalized poisonings have a pronounced CNS depression on admission. The mortality rate among poisonings presenting unresponsive was at least five times higher than the overall mortality from acute poisoning.

7 POPULAR SCIENCE SUMMARY IN SWEDISH

När en medvetslös patient kommer till akutmottagningens akutrum är det en stor utmaning för mottagande läkare att så snabbt som möjligt välja diagnostisera tillståndet och starta nödvändig behandling. Ungefär 1% av alla patienter som kommer till medicinakuten är medvetandesänkta. En målsättning med denna avhandling var att öka kunskaperna om orsaker till medvetslöshet samt att undersöka kort- och långtidsprognos. Ytterligare en målsättning var att beskriva lätt identifierbara egenskaper hos medvetslösa patienter som med hög sannolikhet tillåter indelning av bakomliggande orsak till ett fokalt (t ex stroke) eller metabolt tillstånd (t ex förgiftning). Resultaten grundar sig i huvudsak på en grupp om 938 patienter som identifierades prospektivt på Södersjukhuset, Stockholm och Karolinska sjukhuset, Solna under åren 2003-2005. Patienterna identifierades på akutrummet av sjuksköterskor som gjorde bedömning av vakenheten enligt en bedömningsskala för medvetandepåverkade patienter, Glasgow Coma Scale (GCS) där 3 poäng innebär djupast tänkbara medvetslöshet och 15 poäng innebär full vakenhet. Patienter med en GCS poäng på 10 eller lägre inkluderades i studien. Ingen intervention gjordes utan enbart observation ingick i studien och de läkare som handlade patienterna kände inte till undersökningen.

Resultaten grundar sig på uppgifter från journalsystem, folkbokföringsregistret samt den GCS mall som fylldes i vid inklusionen. I delstudie IV kompletterades materialet genom en retrospektiv undersökning av 1314 förgiftningsfall som inkom till Södersjukhuset under åren 2009 och 2010.

I delstudie I och IV framkom att förgiftning var den vanligaste orsaken till medvetslöshet på medicinakuten (38%), i synnerhet hos yngre patienter. Av de förgiftade patienterna var 80% under 40 år. Ungefär en tredjedel av alla förgiftningspatienter som kommer till akuten har en uttalad medvetandesänkning. Prognosen för dessa medvetslösa förgiftade patienter visade sig vara allvarlig. De hade mer än fem gånger så hög sjukhusdödlighet som förgiftningsgruppen i sin helhet.

I delarbete II framkom att sjukhusprognosen var avhängig både graden av medvetslöshet (ju djupare desto sämre prognos) och orsaken till densamma. Dödligheten varierade från 0,9% i epilepsigruppen till 72% i gruppen där medvetslösheten berodde på cirkulationssvikt. Långtidsprognosen för de som skrevs ut levande var däremot enbart beroende av orsaken och inte av graden av medvetslöshet vid ankomst till sjukhuset. Den genomsnittliga 2-årsdödligheten i hela populationen av levande utskrivna var 43%. Patienterna med förgiftningsdiagnos hade en 2-årsdödlighet på 11,5% jämfört med patienterna med cancer som hade en 2-årsdödlighet på 83%.

I delstudie III delades patienterna in i två grupper beroende på metabol eller fokal orsak till medvetslösheten. Vi fann då att lätt identifierbara faktorer som ålder, blodtryck och fynd vid neurologisk undersökning var avgörande för om medvetslösheten berodde på metabol eller fokal bakomliggande orsak. Patienter yngre än 51 år med ett systoliskt blodtryck under 151 mmHg och frånvaro av fokal fynd hade med 96%-ig sannolikhet ett metabolt bakomliggande tillstånd.

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