

*Janne Liisanantti*

# ACUTE DRUG POISONING: OUTCOME AND FACTORS AFFECTING OUTCOME

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*JANNE LIISANANTTI*

**ACUTE DRUG POISONING:  
OUTCOME AND FACTORS  
AFFECTING OUTCOME**

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***Abstract***

Patients with acute drug poisonings are common in emergency departments and hospitals. Patients typically ingest medical products, most commonly psychotropic drugs that lead to intoxication. The outcome is usually good and hospital stays are short, even among patients requiring intensive care. Complications such as aspiration pneumonia can prolong hospital stays. Acute mortality is low (usually less than 5%) but repetition of self-harm is common and long-term mortality is high.

The aim of this study was to evaluate the outcome of drug poisoned patients and the factors associated with unfavourable outcome, including morbidity, length of intensive care unit (ICU) and hospital stays, repetition of drug poisonings, and mortality.

The study population consisted of patients treated in Oulu University Hospital due to acute drug poisoning between 1985–2006 and drug poisoned patients in the data base of the Finnish Consortium intensive Care Data.

In the first part of the study 276 hospitalised self-poisoned adolescents were examined retrospectively from the patient records for acute contributing risk factors before the intake. Patients with such risk factors had higher rates of depression, non-ethanol poisonings and repetition of self-poisoning within one year.

The second part of the study included 257 acute drug-poisoned adult patients requiring intensive care. The factors associated to aspiration pneumonia were evaluated retrospectively. Of these, 28.4% had aspiration pneumonia. Pre-hospital intubation of the comatose patients was associated with lower number of aspiration pneumonias. The third study evaluated 2755 drug-poisoned patients requiring intensive care for risk factors for prolonged ICU length of stay (LOS) using national intensive care database. Factors associated with prolonged stay were respiratory failure, renal dysfunction and lowered platelet count on admission. The hospital mortality in these studies ranged from 0 to 1.6%.

The fourth study evaluated the long-term mortality and causes of deaths of 3709 patients admitted to Oulu University Hospital due to acute drug poisoning between 1985 and 2000. The all-cause mortality was recorded at the end 2009 and patients were compared to age- and sex-matched controls. Mortality among the study population was 30.6% compared to 13.6% for the controls.

In conclusion, patients admitted to hospital due to acute drug poisoning have good short-term outcomes. Factors associated with prolonged ICU LOS were aspiration pneumonia, respiratory failure on admission, lowered platelet count on admission and renal dysfunction on admission. Impulsive self-poisonings among adolescents are associated with psychopathology and repetitions. Patients with acute drug poisonings have high long-term mortality.

**Keywords:** aspiration pneumonia, drug poisoning, emergency medical services, intensive care, mortality, outcome, self-harm, suicide



## **Liisanantti, Janne, Akuutin lääkeainemyrkytyspotilaan ennuste ja ennusteeseen vaikuttavat tekijät.**

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### ***Tiivistelmä***

Myrkytyspotilaat ovat yleinen potilasryhmä päivystyksissä ja sairaaloissa. Sairaalahoitaisen, akuutin lääkeainemyrkytyksen ennuste on hyvä ja jopa tehohoitoa vaativat potilaat selviävät lyhyellä sairaalahoitajaksolla. Komplikaatiot, kuten mahan sisällön hengitysteihin joutumisesta aiheutuva keuhkokuume (aspiraatiokeuhkokuume) pitkittävät hoitoa. Kuolleisuus hoitojakson aikana on yleensä alle 5 %, mutta pitkäaikaiskuolleisuus näillä potilailla on merkittävä.

Tutkimuksen tarkoituksena oli selvittää akuutin lääkeainemyrkytyspotilaan ennustetta ja ennusteeseen vaikuttavia tekijöitä. Ensimmäisessä osatyössä tutkittiin 276 nuoren myrkytyspotilaan myrkytystapahtumaan vaikuttaneita akuutteja riskitekijöitä. Potilaat, joilla oli riskitekijöitä, olivat useammin masentuneita ja heillä oli enemmän uusintakäyntejä myrkytysten vuoksi vuoden sisällä. Toisessa osatyössä selvitettiin aspiraatiokeuhkokuumeen yleisyyttä 257 tehohoitoa tarvitsevalle lääkeainemyrkytyspotilaalla. Potilaista 28,4 % sai aspiraatiokeuhkokuumeen. Ennen sairaalaan tuloa suoritettu hengitysteiden varmistaminen hengityspotkella (intubaatio) pienensi aspiraatiokeuhkokuumeen riskiä merkittävästi verrattuna niihin, jotka intuboitettiin vasta sairaalassa. Kolmannessa osatyössä tutkittiin 2755 myrkytyspotilaan riskitekijöitä pitkittyneeseen tehohoitoon. Hengitysvajaus, munuaisten toiminnan vajaus ja matala veren verihiutalearvo sairaalaan tullessa olivat pitkittyneen hoidon riskitekijöitä. Kuolleisuus hoitojakson aikana oli näissä kolmessa tutkimuksessa 0–1,6 %. Neljännessä osatyössä tutkittiin 1985–2000 OYS:ssa hoidettujen myrkytyspotilaiden pitkäaikaisennustetta ja kuolinsyitä. Kuolleisuus vuoden 2009 loppuun mennessä oli 3709 potilaan joukossa 30,4 %, kun vastaava kuolleisuus ikä- ja sukupuolivakioitujen verrokien keskuudessa oli 13,6 %. Kaikki kuolinsyyt olivat yleisempiä tutkimusjoukossa verrattuna verrokkeihin.

Yhteenvedon voidaan todeta että akuuttien myrkytyspotilaiden ennuste on hyvä akuutissa vaiheessa. Aspiraatiokeuhkokuume on yleinen komplikaatio myrkytyspotilailla ja se on osittain vältettävissä hengitystien varhaisella varmistamisella. Impulsiivinen käytös nuorella myrkytyspotilaalla assosioituu psykopatologiaan ja uusintamyrkytyksiin. Myrkytyspotilaan pitkäaikaisen ennusteen on huono. Kuolleisuus ennaltaehkäistäviin syihin, kuten itsemurhiin sekä sydän- ja verisuonitauteihin, on huomattava.

*Asiasanat:* ensihoito, itsemurha, itsetuhokäyttäytyminen, kuolleisuus, myrkytykset, tehohoito





To the ones I love the most  
and  
For those loved least in this world

*“The future is uncertain and the end is always near”*  
Jim Morrison



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Oulu March 2012

Janne Liisanantti

## Abbreviations

AC	Activated charcoal
AP	Aspiration pneumonia
APACHE II	Acute physiology and chronic health evaluation II; A scoring system for severity of illness used in intensive care medicine
CNS	Central Nervous System
DSH	Deliberate self-harm
ED	Emergency department
GCS	Glasgow Coma Scale
ICD-9&10	International Clasification of Diseases; International diagnose coding for diseases published by WHO
ICU	Intensive-care unit
LOS	Length of stay
OR	Odds ratio
SOFA	Sequential organ failure assessment score; Organ dysfunction and failure based severity of illness scoring used in intensive care medicine



## List of original publications

- I Liisanantti JH, Ala-Kokko TI, Dunder TS & Ebeling HE (2010) Contributing factors in self-poisoning leading to hospital admission in adolescent in Northern Finland. *Substance Use & Misuse* 45(9): 1340–1350
- II Liisanantti J, Kaukoranta P, Martikainen M & Ala-Kokko T (2003) Aspiration pneumonia following severe self-poisoning. *Resuscitation* 56: 49–53
- III Liisanantti JH, Ohtonen P, Kiviniemi O, Laurila JJ & Ala-Kokko TI (2011) Risk-factors for prolonged intensive care unit stay and hospital mortality in acute drug-poisoned patients: An evaluation of the pshysiologic and laboratory parameters on admission. *Journal of Critical Care* 26: 160–165
- IV Liisanantti JH, Ohtonen P, Kortelainen M-L & Ala-Kokko TI (2011) L-term mortality in patients hospitalized due to acute drug-poisoning: 14-years follow-up study with controls. Manuscript





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# 1 Introduction

The patients with acute drug poisoning are relatively common in hospitals, usually require relatively simple care and have good short-term outcome. However, some of these patients are at risk of acute morbidity and poor long-term outcome. In Oulu University Hospital, for example, approximately 400 of the 32 000 emergency department admissions that lead to hospitalisation each year are due to acute poisonings. Approximately 150 patients are admitted to the Intensive Care Units (ICU) of Oulu University Hospital each year, which represents 6% of the roughly 3000 annual ICU admissions.

In most cases, the needed care is symptomatic, the hospital lengths of stays are less than two days and the primary outcome is good (Beautrais 2003, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, McGrath 1989, Satar & Seydaoglu 2005, Thomas *et al.* 1996a) The substances used in self-poisonings vary depending on the area and the culture. Typical agents used in self-poisonings include pharmaceutical products, mostly psychoactive drugs and paracetamol (acetaminophen), pesticides, rodenticides, herbicides, household chemicals, and illegal street drugs. Alcohol intake is often associated with self-poisonings. In Western Europe and Finland, the majority of self-poisonings involve pharmaceutical products. In contrast to the rest of the Western world, ethanol intake is more frequently associated with drug poisonings in Finland, accounting for up to 67% of patients (Hovda *et al.* 2008, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Limjindaporn 2010, Satar & Seydaoglu 2005, Sharif *et al.* 2003, Thomas *et al.* 1996a).

Patients admitted to hospital due to acute self-induced drug poisoning present various types of motivation. Some poisonings are accidental, mostly among children or accidents in recreational use and in self-medication. Intentional ingestions related to suicide attempts and other deliberate self-harm (DSH) are also common (Burillo-Putze G *et al.* 2003, Hawton & Harriss 2006, Hawton & Harriss 2008, Hovda *et al.* 2008, Sharif *et al.* 2003). Hospital mortality among these patients, even among those requiring intensive care, is low, usually less than 5% (Heyerdahl *et al.* 2008a, Lam *et al.* 2010, Limjindaporn 2010, Satar & Seydaoglu 2005). On the other hand, drug poisoning is sixth common cause of death in Finland but most of the people dying from drug poisoning never reach hospitals (Statistics Finland 2011).

Patients admitted to hospital due to acute drug poisoning often have previous DSH and readmissions occur due to self-poisonings (Lapatto-Reiniluoto *et al.*

1998, McGrath 1989, Thomas *et al.* 1996a). Furthermore, in contrast to the low hospital mortality, long-term follow-up studies show increased mortality of up to 30% during follow-up periods of 10–15 years among patients admitted to hospital due to deliberate self-harm or suicidal attempts at a relatively young age (Nordentoft *et al.* 1993, Owens *et al.* 2005, Rygnestad 1997, Suokas *et al.* 2001). Natural and unnatural causes of deaths both occur and overall mortality due to acute poisonings is also high and, especially in younger age groups, poisoning-related deaths play a major role (Centers for Disease Control and Prevention (CDC) 2007, Kivisto *et al.* 2008c, Nordentoft *et al.* 1993, Owens *et al.* 2005, Rygnestad 1997, Steentoft *et al.* 2001).

It has been stated that it is difficult to recognise patients' risk for both increased short- and long-term morbidity and mortality. This is because the reported hospital stays are short, which complicates screening, and because of the patients' unreliable medical history (Heyerdahl *et al.* 2008b, Lapatto-Reiniluoto *et al.* 1998, Pohjola-Sintonen *et al.* 2000). It seems that it is essential to prevent deaths due to acute morbidity during hospital stays, as well as later in life, since acute mortality due to acute drug poisonings is low among hospitalised patients without complications.

The present study was undertaken to evaluate factors related to both short-term and long-term outcomes in order to obtain information for improving care in this patient population. More specifically, the study aimed to evaluate the risk factors for unfavourable outcome in acute drug-poisoned patients, including short- and long-term morbidity and mortality using cohorts of acute, drug-poisoned paediatric and adult patients from Oulu University Hospital (Oulu, Finland) and the national intensive care registry (the Finnish Consortium of Intensive Care Data, Tieto Health Care Finland, Intensium Ltd.). The study's main focus is on poisonings due to medical products as well as illegal street drugs, with or without ethanol intake. The study does not cover poisonings due to toxic alcohols, herbal, animal, carbon monoxide, herbicides, rodenticides and pesticides. The study's hypothesis is that at-risk patients can be identified and that management of these risks may have an impact on the outcome.

## **2 Review of the literature**

### **2.1 Definitions**

Poisoning is a condition in which a substance that is injurious to physical health or can cause death is taken orally, inhaled, transdermally or parenterally. Normally used substances such as water can be poisonous depending the amount ingested (Shiel & Stöppler c2008). Acute drug poisoning is the most common form of deliberate self-harm (DSH) in the western world. DSH is an act whereby an individual has the intention to cause physical or psychiatric harm to himself or herself but not necessarily with suicidal intent (Fox & Hawton 2004).

Drug poisoning is a condition where substances that are used normally in medical practice are ingested in an inappropriate manner, usually in deliberate self harm, recreational use or through medical error. Drug poisoning can also refer to the use of illegal street drugs but in this study term “drug poisoning” includes medical products unless otherwise stated. Self-poisoning is a condition in which an individual takes a poisonous substance, either accidentally or with suicidal, DSH or recreational intent (Fox & Hawton 2004, ICD-10 2004, Shiel & Stöppler c2008).

Intoxication is a condition that may follow ingestion of a poison or an inappropriate use of a drug and can be described as an altered level of consciousness, mental status or physiology (ICD-10 2004).

### **2.2 Epidemiology**

#### **2.2.1 Incidence**

##### *Incidence of hospitalisations*

Not all contacts with the health care system due to acute poisoning lead to hospital admission. The proportion of patients treated by ambulance service or solely on emergency departments varies, depending on the area, from 20% to 80%. (Hovda *et al.* 2008, Hutton *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998). Acute drug poisonings account for between 0.7 and 15% of all emergency department admissions in different locations (Burillo-Putze G *et al.* 2003, Koliou *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009). Intensive care is

required in 3.7–40% of patients hospitalized due to drug poisoning. The highest rates of intensive care are in the Nordic countries, with the highest rate, 40%, in Oslo, Norway. In Finland, approximately 10% of the patients admitted to hospital from the emergency department due to acute poisoning required intensive care (Burillo-Putze G *et al.* 2003, Heyerdahl *et al.* 2008a, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009). Approximately 5.2% of all ICU admissions in Finland are due to acute drug poisoning (Tieto Health Care 2011). The incidence of hospital admissions due to drug poisonings in the Nordic countries is reported to be 2–2.5/1000 inhabitants per year. In 2002, the incidence of hospital discharges in Finland following acute poisonings was 1.5/1000 inhabitants, which is lower than in the other Scandinavian countries. (Andrew *et al.* 2008, Hovda *et al.* 2008). However, this result can be biased due to coding system.

It has been reported that 50–60% of patients admitted to hospital due to acute drug poisonings are female (Burillo-Putze G *et al.* 2003, Exiara *et al.* 2009, Hovda *et al.* 2008, Hutton *et al.* 2010, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009).

### *Incidence of drug poisoning deaths*

Most of the deaths from acute drug poisoning occur outside the hospital environment. (Bjornaas *et al.* 2010, Kapur *et al.* 2005). The reported incidences of poisoning-related deaths are 15.6/100,000 inhabitants per year in the United States (Bohnert *et al.* 2010), and there has been an increase in incidents over the years, especially due to opioid toxicity (Bohnert *et al.* 2010, Centers for Disease Control and Prevention (CDC) 2009, Warner *et al.* 2009) In 2004, the rate of unintentional poisoning deaths in the US was 4.7 in females and 9.5 in males per 100 000 inhabitants and was the second commonest cause of accidental death, after traffic accidents (Centers for Disease Control and Prevention (CDC) 2007). Most deaths are due to accidental poisonings and occur most often among people aged 30 or over (Bohnert *et al.* 2010).

The overall incidence of poisoning-related deaths in Finland in 2002 was 16.6/100 000 inhabitants, which is approximately 50% higher than in the other Nordic Countries or the United Kingdom (Andrew *et al.* 2008, Health Statistics Quarterly 2007) In Finland, the incidence of non-alcohol poisoning deaths was 6.8 in males and 3.2 in females per 100 000 inhabitants per year in 2005. Non-alcohol poisonings are the sixth commonest cause of death and the rate has increased over the last 30 years (Kivisto *et al.* 2008c, Statistics Finland 2011).

The annual number of drug poisoning caused deaths in medico legal autopsies in Finland has been approximately 550 between years 2005–2007. The commonest causes of death in post mortem analyzes of drug-poisoning deaths have been opioids and antidepressants. In most cases more than one substance is found and ethanol intake is associated in approximately half of the cases. Nearly half of the deaths are classified suicides (Vuori *et al.* 2009).

### **2.2.2 Agents used in acute drug poisonings**

The most commonly used agents in acute drug poisonings include psychotropic drugs and analgesics, including opioids and non-opioid analgesics (paracetamol, NSAIDs). Medical products for neurological or cardiovascular diseases play a minor role in acute poisonings. In Finland, ethanol use is often associated with drug poisonings. (Exiara *et al.* 2009, Hovda *et al.* 2008, Hutton *et al.* 2010, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009) The studies present heterogeneity since some include illegal street drugs while others do not. Also, some papers include carbon monoxide poisonings as a method of suicide (Buykx *et al.* 2010, Exiara *et al.* 2009, Hovda *et al.* 2008, Hutton *et al.* 2010, Lam *et al.* 2010).

None of the studies except one Norwegian study (Heyerdahl *et al.* 2008b) used toxicological screening and only Lapatto-Reiniluoto *et al.* (1998) and Buykx *et al.* (2010) used prospective patient interviews. This limits the reliability of the epidemiological data on the agents used in acute drug poisonings (Buykx *et al.* 2010, Hovda *et al.* 2008, Hutton *et al.* 2010, Kivisto *et al.* 2008a, Koliou *et al.* 2010, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009).

Table 1 presents the frequencies of the most common agents used in drug poisonings leading to hospital admission in selected countries.

**Table 1. Frequencies of different agents used in drug poisonings.**

Study	Location	Agents used	Multiple ingestions	Alcohol intake
Exiara <i>et al.</i> 2009	Greece	Psychotropic drugs Non-opioid analgesics	-	-
Hovda <i>et al.</i> 2008	Norway	BENDI 18% Ethanol 17% Paracetamole 12% Opioids 7% GHB 7%	62.5%	-
Hutton <i>et al.</i> 2010	Australia	BENDI 37% Paracetamole 10% Antidepressants 8%	30%	34%
Prescott <i>et al.</i> 2009	UK	Non-opioid analgesics 33% Antidepressants 16% NSAID 13% Sedatives and anxiolytics 9%	≈50%	-
Lam <i>et al.</i> 2010 ICU patients	China (Hong Kong)	BENDI 25% TAD 17% Antipsychotics 11% (CO-poisonings included (15%))	49%	-
Lapatto-Reiniluoto 1998	Finland	BENDI 43% Antipsychotics 19% Ethanol 17% Antidepressants 17%	52%	67%

BENDI (benzodiazepines); GHB (gammahydroxybuturate); NSAID (non-steroid anti-inflammatory drug); TAD (tricyclic antidepressants); CO (carbon monoxide)

### 2.2.3 Intake motivation

Acute drug poisonings can be accidental, overdoses in recreational use, DSH behaviour or suicide attempts. The most common motivation is usually deliberate self-harm, including suicide attempts, which ranges from 29–85% of the cases depending on the population. (Hawton & Harriss 2006, Hovda *et al.* 2008, Lam *et al.* 2010) In Norway, 35% of patients presented suicidal intake motivation, 24% presented non-suicidal deliberate self-harm and 36% were drug overdoses (Heyerdahl *et al.* 2008a). Adverse drug reactions in medication occur but less frequently than deliberate self-poisonings (Schwake *et al.* 2009)



#### **2.2.4 Clinical characteristics**

Patients admitted to hospital due to acute self-poisonings suffer the effects and side effects of the drugs that have been ingested. A typical symptom is sedation; it has been reported that 14–35.4% of patients present altered consciousness and 8–18.9% are comatose upon admission. (Alaspaa *et al.* 2005, Exiara *et al.* 2009, Heyerdahl *et al.* 2008a, Hutton *et al.* 2010) The need for pre-hospital intubation was 12% in a Finnish study concerning pre-hospital activated charcoal (AC) administration and 8% of the patients were hypotensive (Alaspaa *et al.* 2005). Cardiac dysrhythmias are common; especially after ingestion of tricyclic antidepressants (von Mach *et al.* 2004) Miosis is typical in opioid intoxications. Extra pyramidal symptoms may occur following intake of antipsychotics (Mokhlesi *et al.* 2003a). Table 2 presents the symptoms of poisonings due to typical agents used in drug poisonings according to the reviews of Zimmermann, Mokhlesi, and Levine (Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Zimmerman 2003).

**Table 2. Typical agents used in acute drug poisonings and clinical manifestations in acute poisoning.**

Agent used in drug poisoning	Symptoms, vital signs
Benzodiatsepines	GABA-receptor mediated CNS depression low doses: sedation high doses: coma and respiratory arrest
Tricyclic antidepressants	Symptoms occur within 6 hours of ingestion including CNS depression, anticholinergic symptoms (mydriasis, fever, delirium, tachycardia, ileus, urinary retention), cardiovascular symptoms (prolonged QRS, QTc and PQ-interval)
SSRIs	Sedation, vomiting, cardiovascular symptoms in severe poisonings (prolonged QRS, QTc-interval, ventricular tachycardia)
Antipsychotics	Sedation, rigidity, seizures in severe poisoning NMS (hypothermia, rhabdomyolysis, rigidity)
$\beta$ -Blockers	Cardiac $\beta$ 2-receptor mediated bradycardia, reduced inotropia, atrio-ventricular and intra-ventricular conduction blocks
Paracetamole	0–24h from ingestion: nausea, vomiting, diaphoresis, malaise 24–48h from ingestion: abdominal pain, elevated liver enzymes (>10 000 IU/l in transaminases) 48–96h from ingestion: liver failure with encephalopathy, coagulopathy, hypoglycemia
Opioids	Opioid-receptor mediated CNS- and respiratory depression. Bradycardia, hypothermia, non-cardiogenic pulmonary edema
Amphetamines	Periferial release of catecholamine and re-uptake inhibition of catecholamine and monoamine oxidation inhibition mediated CNS stimulation (Confusion, anxiety, mydriasis, tachycardia, arrhythmias, myocardial ischemia, hyperthermia, rhabdomyolysis)

CNS (central nervous system); SSRI (selective serotonin re-uptake inhibitor); NMS (neuroleptic malignant syndrome)

## **2.3 General management of drug-poisoned patients**

### **2.3.1 Initial life support**

The care of drug-poisoned patients consists of four elements: initial life support, decontamination, in some cases antidotal therapy and enhanced elimination. (Brooks *et al.* 2011, Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Mokhlesi *et al.* 2003b, Zimmerman 2003)

There is a lack of evidence-based data on initial life support and the management of acute drug-poisoned patients. According to some authors and guidelines, the initial life support consists of airway management and correction of circulatory status. Protecting the airway is essential in order to prevent aspiration and respiratory insufficiency due to lowered consciousness. Arrhythmias and hemodynamic compromises are corrected and managed as would be the case with any patient in critical condition. (Eizadi-Mood *et al.* 2009, Soar *et al.* 2010, Zimmerman 2003)

There is rarely a specific treatment for drug poisoning but the cause of the poisoning should be assessed during the initial life support. There are recommendations for the diagnosis and for the use of different laboratory tests (Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Mokhlesi *et al.* 2003b, Zimmerman 2003). The symptoms of the poisonings are unspecific, the medical history of the patients can be unreliable and in some cases, such as in severe paracetamole poisoning, the symptoms are delayed (Heyerdahl *et al.* 2008b, Pohjola-Sintonen *et al.* 2000, Zimmerman 2003). As the patient is stabilised and recovered from the poisoning, the psychiatric evaluation should be established (Isacsson & Rich 2001).

The Poisoning Centre consultation has been shown to be cost-effective, especially among the patients admitted to hospital with less severe poisonings because it reduces the number of patients admitted to wards from the emergency department (Miller & Lestina 1997, Spiller & Singleton 2011, Vassilev & Marcus 2007).

### **2.3.2 Decontamination**

#### ***Induced emesis***

Ipecac-syrup-induced emesis was previously the recommended method for gastric emptying as it may be less traumatic than gastric lavation and may be performed effectively within one hour from ingestion. Induced emesis is safe only in patients with normal consciousness. (Mokhlesi *et al.* 2003a) The use of ipecac-induced emesis is not beneficial to the outcome. It does not shorten the length of stay or reduce mortality and it probably increases the risks of complications; therefore, it is no longer recommended. (AACT/EAPCCT 2004, Albertson *et al.* 1989, Levine *et al.* 2011, Saincher *et al.* 1997)

#### ***Gastric lavage***

Gastric lavage is a procedure that aims to empty the stomach using a large oro-gastric tube and lavation with saline. This procedure may be used in cases when a large amount of substance is ingested less than one hour ago (Levine *et al.* 2011, Mokhlesi *et al.* 2003a). There is no strong evidence of the impact that gastric lavation has on the outcome, so it is no longer recommended (Levine *et al.* 2011, Pond *et al.* 1995, Saetta *et al.* 1991, Vale *et al.* 2004).

#### ***Whole bowel irrigation***

Whole bowel irrigation is a technique that is used to increase gut motility, through which it decreases absorption and decontaminates the gut from the ingested substance. A non-absorbable polyethylene glycol solution is administered via a naso-gastric tube until the solution has gone through the gut. This technique is recommended in poisonings with substances not absorbed to activated charcoal, such as lithium or iron (Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Tenenbein 1997, Zimmerman 2003). No randomised controlled trials have shown a benefit for outcomes using whole bowel irrigation in acute drug-poisoned patients. In voluntary studies, the use of whole bowel irrigation did not significantly affect the absorption of paracetamol or aspirin (Ly *et al.* 2004, Rosenberg *et al.* 1988).

### *Activated charcoal*

Activated charcoal (AC) is used in drug poisonings to prevent absorption. It acts by adsorbing high molecular weight substances. The AC is produced from charcoal cleaning it from the material and compounds adsorbed in the processed charcoal. AC has a large surface area that is able to adsorb substances. AC can adsorb both ingested substances and molecules from the biliary secretion decreasing the toxin concentration in the entero-hepatic cycle. It is recommended to administer charcoal to patients with acute drug poisoning within one to two hours from ingestion and even later in cases where slow gastric emptying is suspected (Chyka *et al.* 2005, Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Zimmerman 2003). Multiple dose AC is recommended to use in certain conditions and it can be useful in carbamazepine or theophylline poisonings (AACT/EAPCCT 1999, Levine *et al.* 2011).

Several reviews and position papers have recommended the use of AC (Chyka *et al.* 2005, Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Vale 1999, Zimmerman 2003) However, the evidence of the beneficial effect of AC administration in single or multiple dose regimens in drug poisonings on outcome is lacking. Some randomised studies have compared AC to other decontamination methods (Albertson *et al.* 1989), and others have compared multiple or single dose administration (Eddleston *et al.* 2008). In two randomised controlled studies, the use of activated charcoal did not differ from the supportive care (Cooper *et al.* 2005a, Merigian & Blaho 2002).

### **2.3.3 Procedures to enhance elimination**

#### *Alkaline diuresis*

Forced diuresis is used to enhance the elimination of substances excreted renally. Forced alkaline diuresis may be beneficial in salicylate, methotrexate or phenobarbital poisonings but there is a lack of evidence in this regard. Because forced diuresis requires volume load, which can cause oedema and electrolyte disturbances, its use is questionable. Increased urine pH with normal urine output can be safer technique to enhance the elimination of acidous substances (Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Mokhlesi *et al.* 2003b, Zimmerman 2003).

### *Extracorporeal methods*

Extracorporeal methods such as haemodialysis, haemodiafiltration and hemoperfusion can be used to enhance the elimination of toxins. Haemodialysis or haemodiafiltration can be used to improve clearance of water-soluble, low-protein binding substances. Haemodiafiltration is better than haemodialysis for clearing higher molecular weight compounds, but the clearance with haemodialysis is usually higher. Haemodialysis may be beneficial in severe poisonings with high blood concentrations of the toxin. (de Pont 2007, Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Zimmerman 2003)

In hemoperfusion, blood flows through a filter with adsorbable material, such as activated charcoal, and it can adsorb low protein binding molecules such as theophylline (de Pont 2007), but its availability is limited (Shalkham *et al.* 2006). Molecular adsorbent recirculating system (MARS) is a potential method to enhance the clearance of protein bound substances such as phenytoin; however, its availability is low, the costs are high and there is a lack of evidence. Promising results have been shown regarding mushroom poisonings (Kantola *et al.* 2009, Levine *et al.* 2011).

### *Intravenous lipid emulsion*

Intravenous lipid emulsion is a novel experimental technique, mainly studied in local anaesthetic toxicity, that can be used in poisonings with lipophilic agents when other measures are insufficient. The mechanism of its action is partly unknown (Levine *et al.* 2011). There are animal studies with other medical substances in poisonings but no randomised controlled trials (Harvey & Cave 2008, Tebbutt *et al.* 2006)

#### **2.3.4 Antidotes**

Several antidotes are used in acute poisonings such as naloxone in opioid poisoning, flumazenil in benzodiazepine poisonings and digoxin-specific antibodies in digitalis poisoning (Levine *et al.* 2011, Mokhlesi *et al.* 2003b, Zimmerman 2003). A “coma cocktail” is a diagnostic and sometimes therapeutic tool that includes the administration of naloxone, glucose and thiamine in suspected or known acute drug-poisoned patients (Levine *et al.* 2011, Mokhlesi *et al.* 2003a). There is no evidence of coma cocktail’s beneficial effect on the

outcome of drug poisoned patient. In a meta-analysis of six randomised controlled studies, the use of flumazenile in comatose, drug-poisoned suspected patients was beneficial to reverse coma (Ngo *et al.* 2007) but no RCTs show its beneficial effect on outcome. It has been stated that use of flumazenile in comatose acute drug-poisoned patients with unknown agent ingested is not cost-effective (Barnett *et al.* 1999).

The acute medical history of drug-poisoned patients is unreliable (Heyerdahl *et al.* 2008b, Pohjola-Sintonen *et al.* 2000) Therefore, the use of antidotes in cases other than patients with definitive diagnosis of certain poisoning may be harmful and cause complications such as seizures in tricyclic antidepressant poisoning in flumazenile administration (Haverkos *et al.* 1994, Mordel *et al.* 1992, Spivey *et al.* 1993).

Paracetamol is a typical agent used in drug poisonings in other countries than Finland (Hovda *et al.* 2008, Hutton *et al.* 2010, Prescott *et al.* 2009). In overdose, its toxic metabolite n-acetyl-p-benzoquinonimine (NAPQI) production exceeds the elimination, which depends on the amount of glutathione in hepatic cells. N-acetylcysteine (NAC) replaces glutathione and enhances the detoxification of NAPQI. (Brooks *et al.* 2011, Mokhlesi *et al.* 2003b) The use of NAC in severe paracetamol poisoning has been shown to have benefits (Keays *et al.* 1991).

## **2.4 Clinical management**

### **2.4.1 Pre-hospital care**

Pre-hospital care can be classified to basic life support (BLS) and advanced life support (ALS). BLS includes for example non-invasive airway management using oxygen mask and lateral decubitus position to protect airway and oral or rectal medications. ALS includes invasive airway management, intravenous fluids and medications. Highest level of emergency medical service (EMS) is physician lead EMS-team. (Jussila *et al.* 2009, Ryynanen *et al.* 2010). Pre-hospital management of acute drug-poisoned patients has the same basis as the overall care, initial life support and absorption prevention, while taking the clinical history of the patient (Levine *et al.* 2011, Zimmerman 2003). In drug-poisoned patient ALS “stay and play” strategy includes airway management with orotracheal intubation in case of altered consciousness and need for AC administration.

It has been reported that mortality of emergency patients transported to hospital increases with increased transportation distance, especially due to respiratory conditions (Nicholl *et al.* 2007) and ALS may be beneficial in such conditions (Ryynanen *et al.* 2010). There is a lack of evidence regarding the impact that pre-hospital management has on the outcome of drug-poisoned patients. There is evidence that complications such as aspiration pneumonitis increase mortality and prolongs hospital LOS (Christ *et al.* 2006, Isbister *et al.* 2004). However, there are no randomised controlled studies that advocate pre-hospital intubation and, on the other hand, intubation in a pre-hospital setting in acute drug-poisoned patients may be difficult to perform and involve potential complications (Adnet *et al.* 1998a, Adnet *et al.* 1998b, Megarbane *et al.* 2010). In the Scandinavian guidelines for pre-hospital airway management tracheal intubation is recommended to be performed only by anesthesiologist (Berlac *et al.* 2008).

Some guidelines recommend administering activated charcoal within one hour after ingestion, unless it will not delay the transportation (Levine *et al.* 2011, Mokhlesi *et al.* 2003a, Wax *et al.* 2005). The use of activated charcoal in a pre-hospital setting seems to be safe and, in most cases, possible to perform if ALS-level team is providing the care (Alaspaa *et al.* 2005). There is a lack of evidence from randomised controlled studies supporting the use of pre-hospital activated charcoal administration to improve outcomes of acute drug poisoned patients.

#### **2.4.2 Intensive care**

Between 3.7 and 40% of patients admitted to hospital are in need of intensive care (Burillo-Putze G *et al.* 2003, Heyerdahl *et al.* 2008a, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009). Acute drug-poisoned patients account for between 3 and 13% of the patients treated in ICUs (Cengiz *et al.* 2006, Henderson *et al.* 1993, Lam *et al.* 2010). In the Finnish intensive care database the corresponding proportion was 5.2% 2010 (Tieto Health Care 2011).

The need for intensive-care treatment in acute drug-poisoned patients is mainly to stabilize the patient's physiology, for special treatment to eliminate the substance that requires the intensive-care setting and to manage the complications of poisoning such as pulmonary and cardiovascular complications (de Pont 2007, Isbister *et al.* 2004, Mokhlesi *et al.* 2003a, Mokhlesi *et al.* 2003b, Zimmerman 2003). The most common organ dysfunction is an altered level of consciousness



and patients present relatively low APACHE II scores, ranging from 8 to 15 (Christ *et al.* 2006, Lam *et al.* 2010)

## **2.5 Outcome**

### **2.5.1 Short-term outcome**

#### *Length of hospital and ICU stay*

Patients admitted to hospital due to acute poisoning usually require short-term treatment. Hospital LOSs are reported to be one to three days (Christ *et al.* 2006, Exiara *et al.* 2009, Lam *et al.* 2010, Satar & Seydaoglu 2005). For those who require ICU treatment, the average ICU LOS is approximately 1 day (Christ *et al.* 2006, Lam *et al.* 2010). Factors associated with prolonged hospital and ICU stay are reported to be advanced age of the patient, unintentional intake of substance, critical condition on admission, and complications (Christ *et al.* 2006, Isbister *et al.* 2004, Lam *et al.* 2010, Satar & Seydaoglu 2005). Consultation with the Poisoning Centres is reported to shorten the hospital stay (Vassilev & Marcus 2007)

#### *Complications*

The complication rate among patients hospitalised due to acute drug poisoning was 18% in a Norwegian study (Heyerdahl *et al.* 2008a). Among ICU-treated patients, the most common complications leading to prolonged ICU and hospital stay have been pulmonary complications (11–17%), rhabdomyolysis (11%), and seizures (5.1–8%) (Christ *et al.* 2006, Eizadi-Mood *et al.* 2009, Lam *et al.* 2010). Risk factors for pulmonary complications include lowered consciousness on admission, opiate ingestion, and delay from the ingestion to the hospital admission (Christ *et al.* 2006, Isbister *et al.* 2004).

#### *Hospital and ICU mortality*

Hospital and ICU mortality rates among patients admitted to hospital due to acute drug poisoning are both low. The hospital mortality rate of patients with acute drug poisonings is reported to be 0.2–5.8% (Burillo-Putze G *et al.* 2003, Cengiz

*et al.* 2006, Christ *et al.* 2006, Exiara *et al.* 2009, Lam *et al.* 2010, Satar & Seydaoglu 2005). Pulmonary complications raise the mortality rate to 4.3–8% (Christ *et al.* 2006, Isbister *et al.* 2004). Since the mortality due to acute drug poisonings is low, it is difficult to establish the definitive risk factors for hospital mortality.

### **2.5.2 Long-term outcome**

In general, patients admitted to hospitals due to acute drug poisonings have a high number of readmissions due to poisonings (Hovda *et al.* 2008, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009). Patients admitted to hospital due to drug poisoning require psychiatric care for both in acute setting and in long term. The number of patients admitted to psychiatric care following acute drug poisoning varies from 29% to 47% (Carter *et al.* 2006, Jo *et al.* 2011). In an English material patients admitted to hospital due to acute drug poisonings often have psychiatric diagnoses and treatment. (Haq *et al.* 2010) In patients admitted to hospital due to DSH, most of the costs during the first year following the episode of hospital treated DSH were associated with psychiatric care (Sinclair *et al.* 2011).

Few studies have addressed the long-term outcome following acute drug poisoning. The reported non-suicidal and all-cause mortality rate during the up-to-15-year follow-up period is 4.2–33% for both natural and unnatural causes (Carter *et al.* 2005a, Nordentoft *et al.* 1993, Owens *et al.* 2005, Rygnestad 1997, Suokas *et al.* 2001). Other studies have shown increased mortality in patients with all forms of DHS and suicide attempts. Among these patients, the most common method of self-harm is acute drug poisoning. (Beautrais 2003, Hawton & Harriss 2006, Ostamo & Lonnqvist 2001)

Risk factors for natural causes of death following hospitalisation due to acute drug poisonings are advanced age, affective disorder, and discharge to nursing home (Carter *et al.* 2005a). Risk factors for unnatural death include alcohol and drug abuse, schizophrenia, and prescription of SSRI- medication (selective serotonin re-uptake inhibitor)(Carter *et al.* 2005a). The increasing medical severity of repeated poisonings is reported to be a risk factor for suicide (Carter *et al.* 2005b).

### **2.5.3 Quality of life**

Patients admitted to hospital due to acute self-induced drug poisoning or other forms of DSH have poor long-term outcomes. Natural and unnatural causes of death occur, especially suicides (Beautrais 2003, Carter *et al.* 2005a, Cooper *et al.* 2005b, Hawton *et al.* 2006, Suokas *et al.* 2001). Patients with suicide attempts and deliberate self-induced drug poisonings tend to have social and health-related conditions that affect their quality of life; these include depression, substance and alcohol abuse, unemployment, alienation, and history of imprisonment (Rosenberg *et al.* 2005, Rygnestad 1997, Sheikholeslami *et al.* 2009). It is also reported that patients admitted to hospital due to acute self-induced poisoning are often characterised by unemployment and alienation. This may complicate the preventive health care and lead to higher use of expensive acute and emergency visits in these patients with high morbidity and mortality (Bi *et al.* 2010, Rygnestad 1997).

The number of studies on the long-term quality of life of patients admitted to hospital due to acute drug poisonings is limited. In a French multicenter study patients treated in an ICU following suicide attempts tend to have poorer quality of life after six months of hospital discharge than other diagnosed groups (Hurel *et al.* 1997).

## **2.6 Prevention**

### **2.6.1 Primary prevention**

The primary prevention of drug poisonings consists of laws regarding product safety, development of safer drugs, enhanced knowledge, and suicide prevention. The incidence of paediatric poisonings has declined over the years (Gauvin *et al.* 2001, Kivisto *et al.* 2008b). This could be due to the increased role of Poison Centres sharing information and the introduction of child-resistant packaging of pharmaceutical products (Liebelt & DeAngelis 1999, Wolf-Klein 1996). Newer and safer sleeping pills have decreased the mortality caused by barbiturate overdoses over the years (Singh *et al.* 1999, Vuori *et al.* 2009). There have recently been discussions in the USA about limiting prescription-free doses and re-labelling packages of paracetamol, which is the leading cause of hospital admissions due to self-poisoning. (Cox *et al.* 2011, FDA 2010)

In primary prevention of suicides, it is important to recognise risk patients in advantage and provide good mental health care. (Anderson & Jenkins 2005, Mann *et al.* 2005)

### **2.6.2 Secondary prevention**

Patients admitted to hospital due to acute drug poisonings face high long-term risk of death for both natural and unnatural causes of death. Suicides are common among these patients. (Beautrais 2003, Carter *et al.* 2005a, Cooper *et al.* 2005b, Suokas *et al.* 2001) Patients with acute drug poisonings admitted to hospital have different needs with regard to psychiatric intervention; psychiatric consultation is recommended and most patients are willing to undergo an evaluation (Isacsson & Rich 2001, Kudo *et al.* 2010, Suominen *et al.* 2004).

Studies on the secondary prevention of acute drug poisonings concern suicide prevention and repetition of self-harm. Although there are several psychiatric approaches, no studies have been performed with long-term outcome measures and none have been conducted regarding the prevention of non-suicidal morbidity and mortality of these patients. The endpoints of the studies done are most often the repetition of suicidal behaviour or mental well being. Brief psychodynamic therapy and cognitive psychotherapy after an episode of DSH decreases the repetition rate significantly (Guthrie *et al.* 2001, Slee *et al.* 2008, Stanley *et al.* 2009). There is a lack of evidence regarding the prevention of natural morbidity and mortality in patients admitted to hospital due to acute drug poisoning.

### **3 Aims of the study**

#### *General aim*

The general aim of this study was to evaluate the outcomes of drug poisoned patients and the factors associated with unfavourable outcomes.

#### *Specific goals*

1. To evaluate acute contributing risk factors for acute poisoning and the impact of these factors on morbidity and repetition of drug poisoning among adolescents.
2. To evaluate the factors associated to unfavourable outcomes (including complications, prolonged LOS and mortality) in patients admitted to ICU due to acute drug poisoning.
3. To evaluate long-term outcomes and causes of deaths among patients admitted to hospital due to acute drug poisoning.



## 4 Patients and methods

### 4.1 Patients

The study population consists of patients admitted to Oulu University Hospital between 1985 and 2006 and patients admitted to all Finnish ICUs due to acute drug poisoning between 1998 and 2004. The study population is introduced in the table 3.

**Table 3. Study population.**

Study	Patients
I	276 admissions in patients aged 12–18 years to Oulu University Hospital due to acute poisoning (alcohols included) between 1 <sup>st</sup> January 1991 and 31 <sup>st</sup> December 2006.
II	257 adult admissions to medical-surgical ICU in Oulu University Hospital due to acute drug poisoning due to psycho pharmaceutical products with or without ethanol intake between 11 <sup>th</sup> November 1989 and 31 <sup>st</sup> December 2000
III	2755 admissions to ICUs in Finland due to acute drug poisoning between 1 <sup>st</sup> January 1998 and 31 <sup>st</sup> December 2004
IV	3709 patients admitted to Oulu University Hospital due to acute drug poisoning between 1 <sup>st</sup> January 1985 and 31 <sup>st</sup> December 2000. Patients were followed until the end of year 2009

For the study III the Finnish Consortium of Intensive Care Data was used. The Consortium was established 1994 and the purpose for the collaboration was to enhance the quality of intensive care by bench marking and enable national research projects. Each participating ICU sends daily data of each admission including demographic data and physiological parameters. The data is validated and corrected before sending to the database. By the end of the year 2007 all the University Hospitals and Central Hospitals in Finland were included in the consortium. The database is managed by Tieto Health Care Finland (Tieto Health Care 2011). The data of the database is not scientifically validated but it has been used in several publications (Niskanen *et al.* 2009, Oksanen *et al.* 2007, Strand *et al.* 2010).

## **4.2 Methods**

### **4.2.1 Patient identification**

Patients were identified using discharge diagnose codes from the hospital discharge registries (I,IV), ICU discharge registry (II) and registry of the Finnish Consortium of Intensive Care Data.

The used diagnose codes were: ICD-9 codes 960–977.9 (ICD-9 2000), National Classification of Diseases codes 9600A–9779X (National Classification of Diseases 1987 1986), and ICD-10 codes F11–F19.9, T36–T50.9 (I,III,IV). For the adolescent study population also alcohol and other chemical but not carbon monoxide codes were included. Following codes were used: ICD-9 980–983.9, National Classification of Diseases 9800A–9879X, and ICD-10 F10–F10.9, T51–T57.9 (ICD-10 2004, ICD-9 2000, National Classification of Diseases 1987 1986)(I).

Drug poisoned patients admitted to the medical-surgical ICU of the Oulu University Hospital were identified from the wards discharge records and patients with positive benzodiatsepine, tricyclic antidepressant or neuroleptic drug urinary screening or other vice suspected or confirmed poisoning due to psycho pharmaceutical products with or without ethanol intake were included to study II.

### **4.2.2 Study design and data collection**

The study design is retrospective, observational clinical study. No interventions were performed and all the collected data is from patient records and database registries. According to the policy of the local ethics committee, approval was not required for study since the data had already been collected for clinical purposes and no interventions were done. A statement from the local ethics committee for the analysis of the adolescent population was obtained. For study IV, statements were obtained from the National Institute of Health and Welfare (THL, Terveyden ja Hyvinvoinnin laitos, Helsinki) and the Office of Data Protection Ombudsman (Tietosuojavaltuutetun toimisto, Helsinki). Following these statements, Statistics Finland (Tilastokeskus, Helsinki) accepted the study protocol and provided the data.



### *Data extraction for studies I and II*

For the first two parts of the study (I, II), patient records of the study population was reviewed by the primary investigator (J.L.). Data was extracted to a structured form and later digitalised and analysed using computer software (SPSS). The extracted data consisted of demographic data, LOSs, outcome, and possible complications. The level of consciousness was obtained if possible and divided into two categories: comatose and conscious. If definitive Glasgow Coma Scale (GCS) scores were not available, the level of consciousness was estimated based on ambulance charts and patient records. The comparable GCS scores were 3–7 for comatose patients and 8–15 for conscious patients. Aspiration pneumonia was defined as a condition within 48 hours from hospital admission with new infiltrates in chest x-ray associated with leucocytosis and fever or purulent tracheal secretions (I,II).

In adolescent population the contributing risk factors before the acute self-poisoning were recorded. (I) The risk factors were defined as acute changes in the patients' health, mental health or social environment that probably affected the ingestion. The contributing risk factors were divided into two categories: risk factor or possible risk and no risk factor.

### *Data extraction for studies III and IV*

Studies III and IV were retrospective registry-based studies. For study III, Tieto Health Care Finland, (the administrator of the Finnish Consortium of Intensive Care Data) provided data for each patient admitted to intensive care units for acute drug poisoning in Finland during the study period. The data consisted of demographic data and SOFA and APACHE II scores and their variables, as well as the ICU and hospital LOSs and outcomes. SOFA and APACHE II scorings are validated and widely used methods predicting outcome (APACHE II) and describe severity of illness (SOFA) during intensive care. Both include laboratory variables as well as physiological parameters routinely used in the intensive care (Strand & Flaatten 2008).

APACHE II scoring includes 12 physiological variables covering circulatory status, respiratory function, renal function and homeostasis. SOFA-scoring includes six organ systems (respiratory, circulatory, renal, coagulation, hepatic and central nervous systems). Each variable is scored from 0–4 depending the severity of the organ dysfunction (Strand & Flaatten 2008). In this study score 0

considered to be normal, 1–2 as an indicator of organ dysfunction and 3–4 for organ failure

In study IV, patients' demographic data was retrieved from the hospital's discharge records and the registry was combined to the mortality registry of Statistics Finland. In the study of long-term mortality age- and sex-matched controls were used. For every patient in the study population, five controls with the same year of birth and same gender but different social security number were randomised by Statistics Finland using their standard procedure.

#### **4.2.3 Ethical issues**

The study consists of four parts (I, II, III and IV), all of which have retrospective design. No interventions were made, which meant that there were no direct health-related risks for the study population. The patients did not receive any direct or indirect benefit from being included in the study. The possible risks for the patients in this design include possible data leaks that could be harmful for the individuals, especially in the first study concerning the limited number of patients and data about the social environment and information on chronic health issues. The data protection was performed using coding of the patients so that patient chart management and statistical analyses were performed without names or social security numbers.

Approval was obtained from the ethical committee of Oulu University Hospital for analyzing the adolescent patients (I) because the data from the psychiatric patient records was used. The local ethical committee approved the study protocol. Studies I, III and IV used the statement of local ethics committee that there was no need for committee approval of the retrospective studies in which the data had been collected for clinical purposes and no interventions were planned.

The study can be considered justifiable from an ethical point of view. Firstly, acute drug poisoning is a common cause of hospital admission. The usual outcome is good but complications cause morbidity. The risk factors for morbidity and the interventions avoiding morbidity have not been well studied. Secondly, all admissions due to acute self-poisonings could be considered unnecessary and avoidable. From an ethical point of view, studies concerning avoidable conditions causing morbidity and mortality are justified as are studies concerning the prevention of these avoidable conditions.

#### **4.2.4 Statistical analyses**

SPSS software (versions 10–18.0, SPSS Inc., Chicago, IL, USA) and SAS for Windows (version 9.1.3, SAS Institute Inc., Cary, NC, USA) were used for the statistical analysis. For studies I and II, the primary investigator did the statistical analyses and for studies III and IV the statistical analysis was performed together with a professional biostatistician. Since the study was designed to be descriptive and consisted of cohorts of patients, the sample size was not calculated. The number of controls needed in study IV was estimated using data from the previous studies showing increased mortality among patients with acute drug poisonings and DSH to gain an equal number of deaths in both groups. (Beautrais 2003, Hawton *et al.* 2006, Nordentoft *et al.* 1993, Ostamo & Lonnqvist 2001)

In studies I, II and III, the data was expressed with means and standard deviations, while in study IV the medians with 25<sup>th</sup> and 75<sup>th</sup> percentiles. In all studies, proportions categorical data was tested using Pearson chi-square. For comparison purposes, the Student's t-test was used and Mann-Whitney was used as a non-parametric test for comparing medians in different groups. P-values less than 0.05 were considered to be statistically significant.

In study II, Odds ratios (OR) were calculated with 95% confidence intervals (95% CI) for aspiration pneumonia. In study III, logistic regression analysis was used to estimate multivariate ORs and 95% intervals of confidence for prolonged ICU stay and hospital mortality.

Study IV presented Kaplan Maier curves for the study population and controls. Log-rank test was used to calculate statistical significance.



## 5 Results

Table 4 introduces the main results of the study.

**Table 4. The main results of the study.**

Study	Aim	Patients	Main results
I	To evaluate acute preceding risk factors before self-poisoning	276 out of 309 admissions aged 12–18 admitted to Oulu University Hospital due to acute poisoning	119 patients (46%) had possible or evident preceding risk factors prior to intoxication, which was associated with non-ethanol poisonings, depression, re-admissions within one year.
II	To evaluate the incidence of AP and risk factors for AP	257 adult patients with acute poisoning due to psychotropic drugs requiring intensive care	73 patients (28.4%) developed AP OR and 95% CI for AP in comatose patients: 2.9 (1.2–7.0) if comatose on discovery, 1.8 (0.6–5.7) if intubated pre-hospital, 3.4 (1.3–98.7) if intubated in the ED
III	To evaluate risk factors for prolonged ICU LOS	2755 adult patients admitted to ICU due to acute drug poisoning	Multivariate OR and 95% CI for prolonged ICU stay (>48h): 3.63 (2.49–5.30) if respiratory failure on admission, 3.34 (2.31–4.83) if renal dysfunction on admission, 3.30 (2.39–4.56) if platelet count < 150 x 10 <sup>9</sup> /L on admission
IV	Evaluate the long-term mortality of patients admitted to hospital due to acute drug poisoning	3709 patients admitted to hospital due to acute drug poisoning between 1985 and 2000, followed until the end of 2009	Mortality among the study population was 30.6%, compared to controls 13.6%, P<0.0001

95% CI (95% confidence interval); AP (aspiration pneumonia); ED (emergency department); ICU (intensive care unit); OR (odds ratio).

### 5.1 Patient characteristics

This study included a total of 9177 hospital admissions (I, II, III and IV). The adolescent population had a total of 276 patients, 142 of whom (51.5%) were

males. Females made up the majority in the number of admissions in the adolescent population, with 167 (56%) admissions out of a total of 309. There were 3011 ICU admissions in the adult population (II, III) of the study, of which 1612 (53.5%) were males.

## **5.2 Contributing risk-factors and acute drug-poisoning**

The study examined the contributing risk-factors before self-poisoning in the adolescent population. Forty-three percent (119) of the 276 patients had a possible or evident preceding risk factor prior to self-poisoning. The contributing factor was evident in 11% of the patients. The most common acute risk factors or possible risk factors were problems with the parents (49 cases) and acute psychiatric crisis (24 cases).

A total of 11.7% of the patients were screened depressive and 5.8% were suicidal. Depressed patients more often had a preceding risk factor before the act and a higher number of readmissions within the year. Ten of the 276 patients (3.6%) had a previously recognised psychiatric condition. Depressive patients were more often female, had intentional intake of the poisonous agent, and had non-ethanol poisoning (II).

## **5.3 Factors associated with unfavourable outcome during the hospital stay**

### **5.3.1 Complications**

Aspiration pneumonia accounted for 28.4% of comatose adult drug-poisoned patients admitted to the ICU. Pulmonary complications were rare among adolescents, with only one case of aspiration pneumonia out of the 309 hospital admissions. Three adolescent patients required short-term dialysis due to acute renal failure, but none required chronic renal replacement therapy.

Pre-hospital airway management decreased the OR for aspiration pneumonia. Administration of activated charcoal to comatose patients without intubation significantly increased the OR for aspiration pneumonia, but gastric lavation or charcoal administration followed intubation did not raise the ORs for aspiration pneumonia (II). Respiratory compromise on admission increased the risk of prolonged ICU LOS (III).

### **5.3.2 LOS**

The hospital LOSs in this study were 1.4–6.8 days and the corresponding ICU LOSs were 0.9–1.9 days. The highest ORs in the multivariate analysis for prolonged ICU stay (>48h) were respiratory failure, renal dysfunction, lowered platelet count and fever on admission (III). Aspiration pneumonia was associated with significantly prolonged ICU LOS and hospital LOS (mean 0.9 days, 95% CI 0.8–0.9 without aspiration pneumonia and 1.9 days, 95% CI 1.3–2.6 with aspiration pneumonia for ICU LOS; the corresponding numbers for hospital stay were 2.8, 95% CI 2.5–3.1 and 6.5, 95% CI 5.3–7.6). Adolescents (I) with drug poisoning had longer hospital LOS compared to those with ethanol poisoning (median 1.5 days vs. 1 day,  $P<0.001$ ).

### **5.3.3 Hospital mortality**

Short-term mortality in this study was low, ranging from no fatalities in adolescent population (I) and 1.6% among patients requiring intensive care (II, III). Risk factors for increased hospital mortality in a limited number of patients (42 deaths) included respiratory and renal failure as well as hypotension on admission (III).

The number of deaths in study II was too low (four cases, 1.6%) to estimate the impact of aspiration pneumonia on mortality.

## **5.4 Long-term outcome**

Repeated drug poisonings were common in the study population, with 21% of patients being hospitalised more than once during the study period (IV). In the adolescent population, 6.8% of the patients were readmitted within one year of the index episode. Patients with predisposing risk factors prior to the self-poisoning episode had a higher number of readmissions, with proportions of 12.5% compared to 4.2% (I).

Long-term mortality among patients admitted to hospital due to acute drug poisoning was 30.6%, compared to 13.6% ( $P<0.0001$ ) controls with the same year of birth and gender during the median 14-year follow-up time. The most common causes of deaths among the study population were cardiovascular causes, poisonings and traumas. A total of 10.8% of the patients committed suicide during the follow-up period, compared to 0.7% in controls ( $P<0.0001$ ). All causes of

death were significantly more common among the study population than the controls, except neoplasms and neurological causes of death.



## 6 Discussion

### 6.1 Main findings

The results of this study confirm that short-term outcomes of the patients admitted to hospital due to acute drug poisoning are good. The rate of hospital mortality among patients was low, even those requiring intensive care, and the hospital LOS was short. The results also confirm that, in contrast to the good outcome in a short time span, the long-term outcomes, such as frequency of repetition of self-harm and long-term mortality, were high.

### 6.2 Strengths of the study and generalisability of the results

This study covers a large field of the outcome of the acute drug-poisoned patients involving contributing factors before self-poisoning (I), pre-hospital care (II), intensive care (II, III), juvenile psychiatry (II) and long-term outcome (IV).

Acute drug-poisoned patients are often admitted to hospitals with multiple ingestions (Hovda *et al.* 2008, Lam *et al.* 2010, Lapatto-Reiniluoto *et al.* 1998, Prescott *et al.* 2009). As noted above, the clinical history of these patients compared to the laboratory screening is unreliable (Heyerdahl *et al.* 2008b, Pohjola-Sintonen *et al.* 2000). The present study (I, III, IV) included patients presenting to the EDs and ICUs with no limitations in terms of the type of drugs ingested or the motivation of intake imitating the typical clinical setting.

Study III included almost all ICUs in Finland presenting heterogeneity in area and type of unit. Accordingly, these results can be considered to be generalised across Finland. The long distances and sparse population in the Oulu University Hospital region compared to many other urban areas decrease the generalisability of the results concerning aspiration pneumonia and pre-hospital airway management. In geographic terms, however, the Oulu region is similar to other areas in northern Scandinavia.

Age- and sex-matched controls were used for study IV, concerning long-term mortality of acute drug poisoned patients, unlike previous studies (Carter *et al.* 2005a, Nordentoft *et al.* 1993, Owens *et al.* 2005, Suokas *et al.* 2001). The number of patients was high compared to other studies conducted on acute drug-poisoned patients and was the largest in Scandinavia (Nordentoft *et al.* 1993, Owens *et al.* 2005, Rygnestad 1997, Suokas *et al.* 2001). The reliability of the

results of study is also good for the law on medico legal autopsy affecting the high rate of autopsies in Finland (31.5% in 2009, Mortality Database of Statistics Finland, [www.stat.fi](http://www.stat.fi)), in contrast to some other countries (Finnish law 459/1973, Pounder 2002).

### **6.3 Patient characteristics**

Unlike reported in other centres, the present study had almost equal number of both genders. The usual reported proportion of female patients is higher. (Burillo-Putze G *et al.* 2003, Hovda *et al.* 2008, Lam *et al.* 2010) The number of drug poisonings with ethanol intake was high (I, II), as reported previously in Finland (Lapatto-Reiniluoto *et al.* 1998); this is in contrast to later reported results from Australia (Hutton *et al.* 2010). The reported repetition rate of self-poisoning has been 4–13% (Hovda *et al.* 2008, Lapatto-Reiniluoto *et al.* 1998), which is similar to the adolescent population of the study but lower than the 21% in the adult population. In contrast to the results in a study from Ireland (Sharif *et al.* 2003), the motivation for intake in the present material (I) was more frequently intentional self-harm (14% vs. 23.5%).

### **6.4 Contributing risk-factors**

Depression, low self-esteem, and lower social class have been reported as risk factors for DSH behaviour (Groholt *et al.* 2000). The acute triggers and contributing factors associated with DSH behaviour have not been well studied. In the present results, most of the patients did not have contributing risk factors before poisoning (I). The most common cause of poisoning leading to hospitalisation of these patients was acute ethanol poisoning associated with recreational use, which reflects the Finnish ethanol-consuming culture.

Adolescents with possible or evident contributing factors before poisoning presented more typical DSH behaviour, including intentional intakes of substances, and more frequent poisonings due to pharmaceutical products. The most common triggers for drug poisoning were problems with parents (I). Impulsive behaviour seems to be associated with age and the acute contributing factors analysed in a Norwegian adult population, which is significantly different from the factors in the present study. The triggers for self-poisoning in the adult population were the need to escape stressful situations and the need for care or attention (Hjelmeland & Groholt 2005).

## 6.5 Short-term outcome and complications

The reported LOS in acute drug poisonings have been short, which is comparable to the present results (I, II, III) (Christ *et al.* 2006, Lam *et al.* 2010, Satar & Seydaoglu 2005). Also, the hospital mortality of patients in the present study did not differ from other published reports from the centres in Europe and Asia (Burillo-Putze G *et al.* 2003, Cengiz *et al.* 2006, Christ *et al.* 2006, Lam *et al.* 2010, Satar & Seydaoglu 2005). The present study involved patients with serious drug poisonings who required intensive care and had relatively short hospital LOS and low hospital mortality. According to the results of this study and other reports, the methods or procedures for reducing the mortality of patients hospitalised due to acute drug poisonings are limited.

A novel finding in the present study was renal dysfunction and lowered platelet count on admission as a risk factor for prolonged ICU stay. Previously, reported risk factors associated with prolonged hospital LOS have been altered consciousness and factors associated with patients and poisoning, such as unintentional poisoning and advanced age (Satar & Seydaoglu 2005, Thomas *et al.* 1996b). However, altered consciousness was a typical finding in the study population (II, III). Up to 60% of the patients presented lowered consciousness. Lowered platelet was associated with prolonged ICU LOS and hospital mortality, which could indicate the development of multiple organ failure. Moreno *et al.* (1999) presented the average time for different SOFA variables to reach the maximum scores in patients with multiple organ failure. In their results, CNS failure developed first but the rest of the variables (except the liver failure) reached the maximum scoring within two to three days (Moreno *et al.* 1999). In the present results, CNS dysfunction, respiratory dysfunction and circulatory dysfunction and failure, defined by SOFA scoring, were common and could be considered as symptoms of the drug poisoning (Alaspaa *et al.* 2005, Heyerdahl *et al.* 2008a). According to this and the present results, renal dysfunction and lowered platelet count on admission can be early signs of developing multiple organ failure that is not masked under the normal clinical condition of drug poisoned patients.

Respiratory failure on admission was associated with prolonged ICU LOS and with hospital mortality (III). This may indicate aspiration-associated complications that have been reported to increase mortality (Christ *et al.* 2006, Isbister *et al.* 2004).

Previously, the proportion of patients with aspiration pneumonia/pneumonitis has been 11–17% (Christ *et al.* 2006, Eizadi-Mood *et al.* 2009, Lam *et al.* 2010). Aspiration pneumonia was more common in the present study, with a rate of 28.4%. One explanation for this could be the lower level of consciousness on admission compared to the other studies; this has been reported as a risk factor for aspiration pneumonia (Christ *et al.* 2006, Lam *et al.* 2010). Also, it is notable that the present study used different criteria for aspiration pneumonia, including new infiltrates in chest x-ray, leucocytosis and fever or purulent tracheal secretions within 48 hours from hospital admission (I, II). Isbister (2004) and Christ (2006) included respiratory dysfunction in their criteria for aspiration pneumonitis.

According to the present results, pre-hospital airway management with tracheal intubation may reduce the risk of aspiration pneumonia (II). However, this result is controversial, since pre-hospital intubation is a difficult technique and is associated with complications; the guidelines recommend that it only be performed by experienced ALS teams (Adnet *et al.* 1998a, Berlac *et al.* 2008, Megarbane *et al.* 2010).

## **6.6 Long-term outcome and mortality**

Previous studies have shown that patients admitted to hospital due to deliberate self-harm have poor long-term outcomes; however, these studies have presented heterogeneity in patients and outcomes. Only Nordentoft *et al.* (1993), Rygnestad *et al.* (1997), Suokas *et al.* (2001) and Owens *et al.* (2005) included all acute drug poisonings and studied all-cause mortality (Beautrais 2003, Carter *et al.* 2005a, Nordentoft *et al.* 1993, Ostamo & Lonnqvist 2001, Owens *et al.* 2005, Rygnestad 1997, Suokas *et al.* 2001). The long-term mortality in the present study (IV) was higher than that reported in most previously published papers, with the exception of the 1993 Danish series (Nordentoft *et al.* 1993, Owens *et al.* 2005, Suokas *et al.* 2001). In addition, a small Norwegian study comparing two cohorts of patients with acute self poisonings showed a mortality rate of 33% during up to 15 years of follow-up (Rygnestad 1997).

The proportion of suicides in the present material (IV) – 10% within 14 years of follow-up – was similar to the rate reported previously in Denmark, but higher than the previous study in Finland, which had a suicide mortality rate of 6.7% during follow-up (Nordentoft *et al.* 1993, Suokas *et al.* 2001). The suicide rate in the present study (IV) was high, even compared to those follow-up studies

involving suicide attempters and all form DSH patients, which had rates of 1–5.6% (Beautrais 2003, Hawton *et al.* 2006, Ostamo & Lonnqvist 2001).

Natural causes of deaths were more frequent in our material (IV), accounting for 34.0% of all deaths. This contrasts with previous follow-up reports on acute drug-poisoned patients, in which the mortality rate due to natural causes accounted for between 4.2% and 13%. Similar to previous reports, cardiovascular causes of deaths were the most common in the present study, albeit with higher incidence (Carter *et al.* 2005a, Nordentoft *et al.* 1993). Rygnestad (1997) noted that a lack of regular income and a low number of contacts with the health care system are typical for self-poisoning patients. This may partly explain the high number of cardiovascular deaths among patients hospitalised due to acute drug poisoning in follow-up studies. These patients may lack preventive measures to reduce the risks of cardiovascular events and long-term care of chronic diseases.

## **6.7 Limitations of the study**

Firstly, the setting is retrospective and observational, which limits the ability to reach firm conclusions. None of the patients were examined clinically for study purposes, and the data of the end-points (I, II) was collected from patient records. However, the study design was able to address the study's aims and the setup enabled the recruitment of an unselected group of patients with real clinical relevance.

Secondly, the low number of patients in study I limits its generalisability, especially in readmissions and the results of those patients evaluated as depressive. However, it was difficult to increase the number of patients in this study because the time span would have increased too much, which would have limited the reliability.

Thirdly, the area of the Oulu University Hospitals' district is large compared to most urban areas in the world and the distances are long. Transportation times may be longer than in other centres, which could have affected the risk of aspiration pneumonia in comatose patients (II). Taking the distance into account could have provided more specific results and could even have made it possible to compare different pre-hospital care strategies. The time span from ingestion to hospital admission was not evaluated and the location or timing of the intubation or the person performing the intubation was not evaluated. On the other hand, it is often impossible in clinical practice to control the time from ingestion to placing the call to the emergency services. Also, unlike other urban areas, in Northern

Finland, there is a limited amount of traffic due to the sparse population, which could reduce the time needed for the patient transportation. The results concerning the risk of aspiration pneumonia should be critically appraised since the EMS has developed over the years in the district area of the Oulu University Hospital (Jussila *et al.* 2009).

Fourthly, registries were used for studies III and IV. None of the patients were evaluated using clinical records. However, all relevant recorded data was extracted to answer the study questions. Patients with a risk of prolonged ICU stay (III) were easily recognised with laboratory and clinical measurements on admission; however, there could also have been possible risk factors for the end points in the clinical setting and examination, which could be even easier to use in clinical practice. Having said that, the aim of the study was to evaluate measurable variables as risk factors. Also, registries were used in study IV and none of the patients were examined and the clinical records were not reviewed. The study design did not allow any data about the patients' possible risk factors for their premature deaths, although this was not the aim of the study.

There is a possibility of errors in the registries' data. The high number of patients limits the effect of possible errors in the results. The registries used in the study are prospectively collected (the Finnish Consortium of Intensive Care Data, Tieto Health Care Finland Intensium Ltd., and the Mortality Registry of Statistics Finland and Oulu University Hospital's discharge registry) and can be considered reliable.

## **6.8 Clinical impact of the results**

According to the present results, the greatest efforts to enhance the outcomes of acute drug poisoned patients should aim to prevent complications leading to prolonged hospital and ICU LOS, as well as preventive measures to prevent further self-harm and premature deaths due to suicides, traumas and, especially, chronic diseases.

The present results show an increased risk of readmissions in adolescents admitted to hospital due to self-poisoning following an acute stress situation. These patients were depressive more often than patients who had no contributing risk factors. Reith *et al.* (2004) evaluated the risk factors for premature death following an episode of self-harm. They found that psychiatric disorders arising from childhood or adolescence are significant risk factors for long-term mortality following suicide attempts at adult age (Reith *et al.* 2004). According to the

results of the present study, all adolescent patients admitted to hospital due to self-poisoning should be screened for impulsive behaviour in order to avoid further self-harm. At-risk patients should be recognised early on during hospitalisation and a psychiatric assessment should be conducted.

This study has shown that respiratory failure on admission determined by the SOFA score was associated with prolonged ICU LOS (III). Furthermore, the study showed in a simple setting that the early airway management decreased the ORs for aspiration pneumonia, which decreases ICU and hospital LOS (II). According to these results, airway management and good care of respiratory function is recommended to shorten the ICU and hospital LOSs, including early airway protection with intubation, which prevents aspiration, and good management of patients' hemodynamic status to prevent organ dysfunctions.

Lowered platelet count and impaired renal function, both of which were associated with prolonged ICU stay and hospital mortality on admission, may indicate the development of multiple organ failure and should be recognised as a possible clinical indicator of a critical condition (III). According to the present results, a good clinical assessment and the correction of the homeostasis of the risk patients is crucial.

Patients with hospital admission due to drug poisoning have poor long term-outcome (IV). Patients should be screened for both psychiatric and somatic risk factors for mortality. Suicides were common among these patients, which means that suicide prevention is essential. According to the present results (IV), risk factors for natural causes of deaths, especially cardiovascular diseases, should also be evaluated and preventive strategies should be established.

## **6.9 Further studies**

This study raises certain issues. Firstly, there is a lack of evidence regarding the strategy of pre-hospital-care of drug-poisoned patients. Study II showed a decrease in OR for aspiration pneumonia if the airway was protected before ER admission. The study did not analyse the distance from the scene to the hospital or the transportation time. Such analysis would be useful for planning pre-hospital strategies, when to “load and go” or “stay and play.” Also, the impact of pre-hospital airway management in comatose drug-poisoned patients should be investigated in randomised controlled setting using the local emergency service. The impact of activated charcoal administration on outcomes in pre-hospital care requires further study.

Secondly, the role of lowered platelet count as a risk factor for both prolonged ICU LOS and hospital mortality in study III is not clear. A prospectively observational study should be conducted in order to characterise the patients in more detail.

Thirdly, the preceding risk factors before self-poisoning should also be screened for the adult population. A randomised intervention study to prevent repetition of self-harm with cognitive psychotherapy or a problem-solving therapy approach should be taken. However, it is likely that this would require a multicentre design, at least in the adolescent population. An intervention study that aims to decrease long-term mortality would require a multicentre design and substantial resources.

Fourthly, study IV leaves a number of open questions. Further studies are needed to screen the risk factors for disease-related mortality, which was high in the study population. Also, the high number of suicides and traumas requires further study. These patients' characteristics could be partly analysed retrospectively from the clinical records. In addition, the high mortality among the patients in study IV raises questions about the use of health-care recourses in these patients. The role of the preventive strategies should be investigated in an intervention setting, although this would also require substantial resources.



## 7 Conclusions

Patients hospitalised with acute drug poisoning have relatively good short-term outcomes. In the long term, however, these patients have a high rate of readmissions due to drug poisonings and a high long-term mortality.

1. Most of the adolescents hospitalised due to acute self poisoning have no acute predisposing risk factors before the poisoning. Adolescents with possible or evident contributing risk factors before poisoning were likely to be depressive and had repeated self-harm.
2. Respiratory failure on admission, as well as aspiration pneumonia, were associated with prolonged ICU stay. Lowered platelet count on admission may indicate developing multiple organ failure and was associated with both prolonged ICU LOS and hospital mortality.
3. Although the hospital mortality of acute drug-poisoned patients is low, the long-term mortality rate in patients admitted to hospital due to acute drug poisoning is more than twice the than age- and sex-matched controls.



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## Original publications

- I Liisanantti JH, Ala-Kokko TI, Dunder TS & Ebeling HE (2010) Contributing factors in self-poisoning leading to hospital admission in adolescent in Northern Finland. *Substance Use & Missuse* 45(9): 1340–1350.
- II Liisanantti J, Kaukoranta P, Martikainen M & Ala-Kokko T (2003) Aspiration pneumonia following severe self-poisoning. *Resuscitation* 56: 49–53.
- III Liisanantti JH, Ohtonen P, Kiviniemi O, Laurila JJ & Ala-Kokko TI (2011) Risk-factors for prolonged intensive care unit stay and hospital mortality in acute drug-poisoned patients: An evaluation of the pshysiologic and laboratory parameters on admission. *Journal of Critical Care* 26: 160–165.
- IV Liisanantti JH, Ohtonen P, Kortelainen M-L & Ala-Kokko TI (2011) High long-term mortality in patients hospitalized due to acute drug-poisoning: 14-years follow-up study with controls. Manuscript.

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