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Inter-hospital transports of critically ill children

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"Live as if you were to die tomorrow.
Learn as if you were to live forever."

Mahatma Gandhi

ABSTRACT

There is an increasing need for inter-hospital transports of seriously ill children as a result of centralization of intensive care for children to dedicated pediatric intensive care units (PICU). This thesis has explored the short-and long-term outcomes of critically ill children after transport by a specialized pediatric transport team to a PICU. In order to investigate the effects of high altitude on transported children, a novel method was introduced to improve the performance of a device for regional oxygen saturation (rSO_2) monitoring working in a transport environment.

In **Study I**, outcomes of critically ill children acutely transported to PICU by a specialized pediatric transport team were retrospectively compared to a control group of children acutely admitted to the same PICU but through other routes. Transported children were younger, sicker and stayed longer in PICU and their use of PICU specific therapies was higher. The transport per se did not increase the risk of death irrespective of transport distance.

Age and risk score related differences in short-and long-term survival among transported patients were evaluated in **Study II**. Median follow-up time for survivors was 4.4 years. Survival in neonatal patients was high after discharge from intensive care, and patients with a Predicted Death Rate (PDR) > 50% showed no mortality after the 30-day follow up. In contrast, there was clinically significant late mortality for the whole cohort, especially in those transported multiple times.

In **Study III** we analyzed the impact of an arterial blood gas sample (i.e. the PaO_2/FiO_2 ratio) on the Pediatric Index of Mortality2 (PIM2) score and its derived probability of death (%). The PIM2 and probability of death only became more accurate if PaO_2/FiO_2 was available for the respiratory admission group, and when a rather high severity of illness was expected.

The aim of **Study IV** was to investigate the applicability of near-infrared spectroscopy (NIRS) data during transport. The ability to distinguish between real and artefact-related events increased considerably by removal of zero values and "floor-effect values" and then using a filtering technique on the NIRS signal to reduce noise in the signal without loss of the original signal structure.

In **Study V**, rSO_2 with NIRS registration from cerebral (rSO_2-C) and splanchnic (rSO_2-A) areas during air ambulance transports of critically ill children was investigated in relation to the effect of altitude ≥ 5000 feet. Both rSO_2-C and rSO_2-A decreased significantly at altitude ≥ 5000 feet compared to baseline in a majority of patients. In most patients rSO_2-A decreased more than rSO_2-C ≥ 5000 feet as expressed by the rSO_2-C/rSO_2-A ratio, which was > 1 in 67% of patients at baseline and > 1 in 77% of patients at altitude ≥ 5000 feet.

In conclusion, this thesis has addressed various aspects of children in need of transport to pediatric intensive care. Acute pediatric inter-hospital transports can be performed without increasing the mortality risk regardless of transport distance if performed by a specialized team. There is a notable late mortality after the 30-day follow up for the transported group as a whole. An arterial blood gas sample for the PIM2 score is only needed when the patient has respiratory reason for admission and a rather high severity of illness is expected. Reliable NIRS data can be obtained during transport when cleared for artefacts and smoothed by a noise-reduction algorithm. Both rSO_2-C and rSO_2-A decreased as an effect of altitude ≥ 5000 feet, however rSO_2-C was better preserved than rSO_2-A

LIST OF SCIENTIFIC PAPERS

I. **Characteristics and outcomes of critically ill children following emergency transport by a specialist paediatric transport team**

Tova Hannegård Hamrin, Jonas Berner, Staffan Eksborg, Peter J. Radell, Urban Fläring
Acta Paediatrica. 2016;105(11):1329-1334

II. **Short- and long-term outcome in critically ill children after acute inter-hospital transport to a Pediatric Intensive Care Unit in Sweden**

Tova Hannegård Hamrin, Peter J. Radell, Urban Fläring, Jonas Berner, Staffan Eksborg
Pediatric Critical Care Medicine, under revision

III. **Unnecessary harm is avoided by reliable paediatric index of mortality2 scores without arterial gas sampling**

Håkan Kalzén, **Tova Hannegård Hamrin**, Lars Lindberg, Ola Ingemanson, Peter Radell, Staffan Eksborg
Acta Paediatrica. 2019;108(4):670-675

IV. **Performance of regional oxygen saturation monitoring by near-infrared spectroscopy (NIRS) in pediatric inter-hospital transports with special reference to air ambulance transports: a methodological study**

Tova Hannegård Hamrin, Peter J. Radell, Urban Fläring, Jonas Berner, Staffan Eksborg
J Clin Monit Comput. 2018;32(5):841-847

V. **Influence of altitude on cerebral and splanchnic oxygen saturation in critically ill children during air ambulance transport**

Tova Hannegård Hamrin, Staffan Eksborg, Jonas Berner, Urban Fläring, Peter J. Radell
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

ABG	Arterial blood gas
AAP	American academy of pediatrics
AAP SOTM	American academy of pediatrics section on transport medicine
AUC	Area under the curve
ANZCTR	Australian New Zealand Clinical Trials Registry
ANZPIC	Australian New Zealand pediatric intensive care
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CRRT	Continuous renal replacement therapy
ECMO	Extra corporeal membrane oxygenation
$ETCO_2$	End-tidal carbon dioxide
FiO_2	Fraction of inspired oxygen
GAMUT	Ground and air medical quality transport database
HbO_2	Oxygenated hemoglobin
HbR	Deoxygenated hemoglobin
ICU	Intensive care unit
IQR	Inter quartile range
LOS	Length of stay
MPE	Mean prediction error
NICU	Neonatal intensive care unit
NIRS	Near-infrared spectroscopy
NO	Nitric oxide
PaO_2	Partial pressure of arterial oxygen
PaO_2/FiO_2	Ratio of partial pressure arterial oxygen and fraction of inspired oxygen
PDMS	Patient data management system
PDR	Predicted death rate
PETS	Pediatric emergency transport service
PIM	Pediatric index of mortality
PICU	Pediatric intensive care unit
PRISM	Pediatric risk of mortality score
RSME	Root mean square prediction error
ROC	Receiver-operator characteristic curve
rSO_2	Regional oxygen saturation
rSO_2-A	Abdominal (splanchnic) regional oxygen saturation
rSO_2-C	Cerebral regional oxygen saturation
SBU	Swedish Agency for Health Technology Assessment and Assessment of Social Services
SMR	Standardized mortality ratio
SpO_2	Peripheral capillary oxygen saturation
SvO_2	Systemic venous oxygen saturation
TT	Tracheal tube

1 INTRODUCTION

The origin of this thesis is a specialized pediatric transport service, PETS (Pediatric Emergency Transport Service), which emanates from The Department of Pediatric Perioperative Medicine and Intensive Care at Astrid Lindgren Children's Hospital, Karolinska University Hospital in Stockholm, Sweden.

PETS, which operates around the clock all year round, covers the entire country of Sweden and performs international retrievals as well when necessary. The transport service started as a project in 2005, after realization that there were many seriously ill children treated in general intensive care units (ICU) in hospitals around Sweden, who would perhaps benefit from care in a dedicated pediatric intensive care unit (PICU).[1] This knowledge, and the clinical apprehension that the actual patient retrieval was difficult and at times a weak link when a child was admitted to the PICU both from hospitals inside and outside the Stockholm County, were the initial reasons for the department to set up a pediatric transport service.

The knowledge and tradition of transporting children from the PICU in Stockholm by fixed wing aircraft was already available and originates from a decision to centralize pediatric cardiac surgery to the university hospitals in Gothenburg and Lund in the 1990's. Today PETS provides transports around the clock, year-round on an acute, semi-acute and planned basis to and from Astrid Lindgren Children's Hospital as well as between external hospitals inside and outside Sweden. In 2008 PETS expanded with a neonatal group for coverage of premature children as well as transports to and from the neonatal intensive care units (NICU) at Karolinska University Hospital. Children transported by Neo-PETS are not included in this thesis.

Team composition includes a PICU consultant and a specialist anesthesia or intensive care registered nurse with a minimum of three years experience in pediatric intensive care or pediatric anesthesia. When the retrieval is expected to be demanding with respect to transport duration, patient status, or if extensive medical equipment is needed, an experienced assistant nurse from the PICU can be added to the team.

The PETS team works as a mobile pediatric intensive care unit. The goal is to provide the same level of care during transport as in the PICU. Depending

on distance, availability and weather conditions a road ambulance or fixed-wing air ambulance is used, more rarely a helicopter. The team helps to stabilize the patient at the referring hospital, initiate PICU-therapies including vasoactive drugs, inhaled nitric oxide, perform interventions such as central and peripheral intravenous access and hemodynamic monitoring, intubation and mechanical ventilation. PETS performed 295 transports in 2018 and is the only specialized pediatric transport organization in Sweden.

With an increased commitment and a growing organization there is a need for continuous development and research. Knowledge about outcomes after inter-hospital intensive care transports in Sweden is scarce and needs to be investigated. Approximately 60% of transports per year made by PETS are long-distance transports performed by air ambulance. In our transport environment cabin pressure can be maintained at near atmospheric pressure (sea level cabin altitude) for a maximum of two hours before a fuel stop becomes necessary. For a routine one-hour transport, maintaining sea level cabin altitude requires 20% more fuel than normal consumption, or roughly 200 liters of extra fuel. Thus, for flights ≥ 2 hours or for fuel economy, cabin pressure is often maintained at a level corresponding to atmospheric pressure at 7000 feet, or 2100 meters. Therefore, the effect of high altitude on critically ill children must be considered in pediatric transport medicine.

2 BACKGROUND

2.1 Centralization of pediatric intensive care

Medical reports from the 1990s state that centralization of intensive care for children to tertiary PICUs improves outcomes, both in decreased mortality and shorter lengths of stay (LOS).[2-6] These reports contributed to the centralization of intensive care for children in many countries including Great Britain, France, The Netherlands, Australia and the US. In Sweden a study performed 1998-2001 showed that less than half of pediatric patients admitted for intensive care in Sweden were cared for in a dedicated PICU, furthermore that LOS longer than 1 day correlated with increased mortality; 3.8%, 4.4% and 5.9% for PICU, adult ICUs and adult university ICUs, respectively.[1] However, this study lacks a severity of illness score and therefore the authors did not speculate on the risk-adjusted mortality in either adult ICUs or PICUs. They identified one group of children though, with short LOS and low mortality who are unlikely to benefit from transfer, and another group with significant mortality and longer LOS who might benefit from transfer to a dedicated PICU.

Today Sweden is centralized with four tertiary PICUs, comparable to the situation in other European countries.[7] The number of PICU beds is however relatively small in Sweden; 1.04 beds/100,000 inhabitants between 1-18 years of age, which ranks Sweden seventeenth out of 23 countries studied in a European survey from 2002.[8] A more recent study which compared 31 European countries and the total number of intensive care beds in relation to population ranked Sweden number 30.[9] National Swedish guidelines introduced in 2015 state that critically ill children under three years of age should be treated in a PICU.[10] The guidelines also recommend that older children suffering from respiratory failure and/or multiple organ failure should be considered for treatment in a PICU, since treatment strategies for these children often differ from those provided in an adult ICU.

An issue which has been investigated is whether physicians working in local hospitals in a centralized region maintain adequate assessment skills in recognition and request of transport for critically ill children.[11, 12] These studies have reported reduced mortality and shorter length of stay in centralized regions with referrals to tertiary PICUs compared to before centralization.

With centralization of pediatric intensive care, it is inevitable that inter-hospital transport of severely ill children and infants will increase and it is of uttermost importance that the transport function is easily accessible and safe without the actual transfer in itself resulting in a worse outcome for the patient.[3, 4]

2.2 The use of specialized pediatric transport teams

Until the late 1980s less than 10 articles had been published on pediatric critical care transport.[13] In 1986 the American Academy of Pediatrics (AAP) published a document titled "Guidelines for Air and Ground Transportation of Pediatric Patients".[14] This was a statement on the requirements of a specialized pediatric transport organization regarding personnel, equipment, mode of transportation etc. Studies from different healthcare systems in the 1990s and early 2000s showed that inter-hospital transports of critically ill children by specialist pediatric transport teams tended to be associated with a lower incidence of technical and physiological adverse events as well as lower patient morbidity compared to when transports were performed by non-specialist teams.[15-18]

In 2006 a systematic review aiming to determine whether the use of specialist transport personnel improves patient hospital outcome in critically ill patients transported to higher specialized centers was published.[19] Studies with only infants or neonatal patients were not included in the review. The authors reported that several studies which included pediatric patients[15, 17, 18] had documented improved patient safety during transport when specialized personnel were used, especially in the most severely ill patients, but that they had not looked at outcomes in the receiving hospitals. One exclusion criteria in the review was absence of a control group. Finally, six studies with a total of 4534 patients were included. One of the included studies concerned pediatric patients.[20] Out of six studies, only one study, which exclusively investigated adult patients, demonstrated a significant difference in mortality at the receiving hospital.[21] The authors summarized that data at that time was insufficient to state if the use of specialist transport personnel improves outcome at the receiving hospital when critically ill patients are transported to a more specialized center.

In 2009 a prospective cohort study of consecutive children (n=1085) showed that the use of a specialized pediatric transport team was associated with improved survival rates after adjustment for illness severity compared to non-specialist teams.[22] The specialized teams also experienced fewer adverse events. There was a 38 times higher presence of one or more unplanned

event during transports performed by a non-specialized team compared to a specialized team (61.0% vs 1.6%). In this study referring hospitals, transport vehicles, command physicians and receiving hospital were the same for the whole study population and the only variable that differed was the transport personnel. The study provided strong evidence that the use of a specialized team can reduce mortality rates as well as adverse events, confirming the initial findings by Edge et al. in 1994 who demonstrated that children transported by specialized transport staff experienced fewer adverse events than those transported by non-specialized teams.[18]

In 2010 a national study from the United Kingdom was published including 16875 children ≤ 16 years consecutively admitted to PICUs in England and Wales during 4 years, after being transported by either a specialist or non-specialist retrieval team.[23] Primary outcome measures were mortality rates in PICU and LOS in PICU among survivors. Multivariable analysis showed significantly lower risk of death when patients were transported by a specialist team compared to non-specialist transport teams. Time spent in PICU was similar in both groups. The findings in this report supported the combination of centralization of intensive care for children and transports by specialized pediatric transport teams.

There is an increasing body of literature that supports the premise that early goal-directed therapy improves outcome in many adult as well as pediatric illnesses, such as septic shock, head injury and trauma.[24-27] A prospective, single center, controlled before-and-after study, n=235, (patients aged 1 month to 17 years), compared study groups prior to and after institution of a goal-directed resuscitation protocol for transport of critically ill children with Systemic Inflammatory Response Syndrome (SIRS) and SIRS-induced shock.[28] The results showed that patients in the two groups did not receive significantly different amounts of fluid resuscitation and only 5% of patients in the goal-directed therapy group received inotropic agents during transport compared to none in the non-goal-directed group. The goal-directed therapy group had a shorter hospital LOS and required fewer initial ICU interventions. The authors noted that a combination of factors leading to overall improved quality of care and enhanced tissue oxygen delivery during transport led to the observed outcome differences.

2.3 Performance of a specialized pediatric transport team

At the Second National Interfacility Transport Medicine Leadership Conference, in 2000, the AAP called for standards for benchmarking and quality indicators for transport organizations.[29] This was also called for by Ramnarayan

in 2009, claiming that without robust indicators it would be impossible to monitor performance.[30] In 2013 an article that summarized the meeting conclusions and consensus views from a National Consensus Conference held by The AAP Section on Transport Medicine (SOTM) was published.[31] It was stated that most programs have local quality indicators, but few have the opportunity to compare successes with others and that transport-specific benchmarks must be established.

To achieve consensus on appropriate neonatal and pediatric transport quality indicators among regional experts and practitioners of neonatal and pediatric retrieval in Ohio (US), and thereby permit comparisons among programs, a project was set up in 2011.[32] By identifying candidate quality indicators through literature review and metrics currently in use by each transport program, consensus was achieved by nominal group technique. A national project was later set up and presented on behalf of the AAP SOTM in 2015.[33]

Initially 82 candidate metrics were considered; by using a so-called modified Delphi technique ultimately 12 metrics achieved consensus as "very important" to transport: 1) Unplanned dislodgement of therapeutic devices, including unplanned extubation 2) Verification of tracheal tube (TT) placement 3) Average mobilization time of the transport team 4) First-attempt TT placement success 5) Rate of transport related patient injuries 6) Rate of medication administration errors 7) Rate of patient medical equipment failure during transport 8) Rate of CPR performed during transport 9) Rate of serious reportable event 10) Unintended neonatal hypothermia upon arrival to destination 11) Rate of transport related crew injury 12) Use of a standardized patient care hand-off.

Some of these 12 metrics will be reviewed in detail here:

2.3.1 Average mobilization time of the transport team

Mobilization time of the transport team defined as: "from the start of the referral phone call to the transport team until the time the transport team is en route to the referral facility".

The team and vehicle activation and mobilization times are components which should always be minimized, but it has been argued that this criterion says more about the organization of the transport team than the actual standard of care that the transport team will be able to give to the patient.[34] Nevertheless the response time, defined as the time from the start of the referral phone call to the time the transport team arrives at the referral hospital, is a parameter which referring physicians understandably enough are

concerned about.[35] The response time has also been pointed out by others to be an important quality indicator but rather difficult to measure since it is affected by many different factors such as geographical distances and conditions, team and vehicle availability etc.[36, 37] Long response times put the sick child at risk and authors have pointed out the importance of providing the local team at the referring hospital with active telephone guidance on continuing management until the transport team has arrived. This can be done both by the transport team and the receiving physicians.[15, 30, 36, 37]

The stabilization time at the referring hospital, that is, the time the transport team requires to get the patient ready for transport is another retrieval time component that has been argued to measure the actual quality of care in critical care transport.[34] The variation of median stabilization times which has been published is wide.[15, 37-41] Reasons for this may be the number and magnitude of interventions performed on site before retrieval, taking into account that not only the intervention itself takes time but also the necessary safety arrangements afterward such as measurement of blood gases and x-rays.[41]

Stabilization is defined as the identification of those factors that, if not properly corrected, may lead to deterioration of the infant's condition during transfer. An adequate stabilization before transport lowers morbidity and improves the chances of survival.

In a study of 2106 pediatric inter-hospital transports performed during a 2-year period, data were prospectively analyzed to examine the effects of patient- and transport related factors on the stabilization time and the effect of stabilization time on 24-hour PICU mortality.[38] The length of stabilization time itself had no negative impact on early PICU mortality, the only independent predictors being the Pediatric Index of Mortality Score (PIM2 score)[42, 43] and the number of major interventions required during stabilization. Results also showed that only PIM2 score, number of major interventions, and referral category (acute vs. non-acute transports) were significant variables affecting stabilization time. The numbers of urgent vital interventions needed upon arrival at destination to tertiary PICU might also indicate inadequate stabilization during transfer.[16, 30]

2.3.2 Rate of serious reportable events

It has been shown that the continuing process of critical incident reporting and review may reduce the number of adverse events during the transfer of critically ill infants.[44]

From Canada, another modified Delphi study was published in 2014.[45]

The aim was to identify and evaluate indicators that represented significant events during pediatric transports, indicators which also would be relevant to future research in pediatric transport. An expert group picked out 57 indicators of which 52 were determined to be relevant, 31 indicators from the transport literature and 21 new indicators, not previously identified in the literature. The authors claimed that with this large number of new indicators future adverse events rates might differ from those previously reported. Some indicators presented by the Canadian group were identical to the Ohio list from 2011, but the Canadian list was much longer. The reason for this disparity was, according to the authors, that their goal aimed for inclusiveness, whereas the Ohio group limited metric selection to 18–24 items and was focused on ease of application.

These consensus-derived definitions[45] of adverse events during inter-hospital transports were adapted in a retrospective study from a single center pediatric, parameter driven, critical care transport provider using administrative and clinical data of 8889 patients and published in 2016.[46] The primary outcome was in-transit critical events, but unfortunately exclusively inter-hospital transports contributed only to 72% of the total amount of transports (n=5672). The additional subjects were a mixture of scene calls and modified scene calls, making any interpretation of adverse events during the transport phase and identification of any associated factors to these events difficult. Authors concluded that the Transport Pediatric Early Warning Score was a poor predictor of critical events during transport.

In 2014, the consensus quality metrics selected by the AAP SOTM were joined with the consensus metrics selected by the Air Medical Physician's Association to create a database for data collection to improve critical care transport: Ground and Air Medical qUality Transport Database (the GAMUT database). It is a free global resource for transport teams to track, report, and analyze their performance on transport-specific quality metrics by comparing it to other programs.[47] Participating air and ground critical care transport programs submit aggregated data on a monthly basis. There is no individual patient- or transport-level information.

2.3.3 Rate of medication administration errors

The pattern of drug administration during inter-facility transports of critically ill children to a PICU has shown that a relatively small number of drugs are used frequently, but the total range of drugs that are used is large.[48]

In a study over 1 year from 1991 it was reported that 70% of patients transported by a combined neonatal and pediatric transport team were given

drugs; most commonly antibiotics (39% of patients), morphine (27%), anticonvulsant drugs (24%), neuromuscular blocking agents (14%), respiratory medications (including bronchodilators and surfactant) (12%), inotropes (11%) and sedatives (8%).[49]

The 2-year data published in 1996 from a combined pediatric and neonatal transport team, where 38% of neonates and 22% of pediatric patients were mechanically ventilated, showed that newborns received antibiotics and morphine more frequently than pediatric patients whereas anticonvulsant drugs and respiratory medications (including bronchodilators) were more commonly administered to pediatric patients.[50]

To investigate if vasoactive drugs could be safely administered via peripheral veins, a retrospective study was published in 2010 where the medical records of 1133 transports of neonates and children to intensive care units were reviewed.[51] The risk for complications increased with higher medication doses (Dopamine 10 vs 15 microgram/kg/min) and longer duration of therapy. Authors concluded that prompt transitioning of vasoactive infusions to a central venous line upon arrival at destination may lead to fewer complications but does not seem to be necessary before transport in transfers with a maximal duration of approximately four hours.

2.3.4 First-attempt tracheal tube placement success

A multicenter retrospective study in 2015 of more than 7000 pediatric and neonatal transport patients investigated first-attempt tracheal tube placement success.[52] This showed a first-attempt intubation success rate for all intubations of 64% and a spread between different transport programs of 35% - 87% first-attempt intubation success rate. Most teams consisted of an emergency medical technician (EMT), a registered nurse (RN), and a registered respiratory therapist (RRT). The lowest figures occurred in programs with simulation only as the way to achieve initial intubation competency. The authors concluded that understanding how certain transport programs achieve high performance is necessary in beginning to develop neonatal and pediatric intubation best practices.

In a single center retrospective chart review from a hospital based neonatal/pediatric critical care transport team researchers aimed to determine risk factors for failed tracheal intubation in neonatal and pediatric transports, n=167.[53] Patients were eligible if they were transported and intubated by the critical care transport team. The transport personnel responsible for transport intubations were respiratory therapists. Patients were categorized into two groups for data analysis: 1) no failed intubation attempts and 2) at least

one failed intubation attempt. There were higher rates of intubation failure in transported neonates compared to transported pediatric patients. The risk seemed to be increased by the lack of benzodiazepine premedication and of a neuromuscular blocking agent. The presence of comorbid conditions was associated with a higher risk of tracheal intubation failure, regardless of age.

A multicenter retrospective study based on data from the GAMUT database reported tracheal intubation attempts by critical care transport teams in 4.7% of a mixed (adult, pediatric and neonatal) cohort of 85704 transported patients.[54] Transfers included both pre-hospital and inter-hospital transports. First attempt tracheal intubation success was lowest in neonatal patients, better in pediatric patients and highest in adult patients. The success was highest when tracheal intubation was performed by adult critical care teams, also among pediatric patients. The presence of hypoxia and/or hypotension during intubation was lower when intubation was performed by adult teams than pediatric teams. The training level or experience of the personnel involved did not appear in the study and the success rates were lower than in-hospital success rates. Authors conclude that identifying factors affecting tracheal intubation success among skilled performers should influence best practice strategies for intubation.

2.3.5 Verification of tracheal tube placement

In a prospective observational study during 18 months, 77 neonatal (34 patients) and pediatric (43 patients) patients were intubated by the respiratory therapist in a hospital based pediatric/neonatal transport team.[55] Both rate of tracheal tube (TT) repositioning and on-scene time were examined. A post-intubation chest x-ray to verify correct TT-placement (mid-tracheal TT position) was performed in 85.7% of patients and showed malposition in 47% of cases, equally distributed between neonates and pediatric patients. Stabilization time was significantly extended for the neonatal group if a post-intubation chest x-ray was taken (average 33 minutes), but not for the older group. Authors conclude that post intubation chest x-ray is informative in this setting and should be performed when feasible before the start of transfer even if the procedure may extend stabilization time.

Capnography is of great importance in confirming endotracheal tube position in critically ill children.[56] Capnography readings might however, especially in pediatric patients, not always be reliable because of tube leakage. In these situations, the arterial CO_2 pressure measured with a blood gas sample gives more information so that ventilator settings can be changed and the blood gas values normalized during transport.[57] Analyzing the difference

in CO_2 tension in mechanically ventilated neonates transported either on ground or in air (helicopter or fixed wing), showed no increased risk of abnormal CO_2 tensions during air transports, but both hypercapnia and hypocapnia were common in both modes of transport.[58]

The usability of blood gas analysis and its influence on therapeutic interventions during inter-hospital pediatric intensive care transport were studied in a prospective observational study of 51 tests performed in 29 patients.[57] Adjustment of FiO_2 based on the blood gas results was required in 45% of the patients before and during transport. The majority of interventions were adjustments of the mechanical ventilation, but low potassium and hematocrit were also detected, and treatment initiated during transfer. Bhatia et al. showed that adjustment of mechanical ventilation was required in 30% of the patients on the basis of the blood gas results obtained before departure from the referring hospital.[59]

To document inter-hospital transport ventilation monitoring practices in severe pediatric traumatic brain injury patients, the use of end-tidal CO_2 ($ETCO_2$) monitoring and blood-gas analysis were retrospectively studied in 34 patients.[60] Results showed that specialized transport teams used $ETCO_2$ monitoring significantly more often than non-specialized teams (90% vs 23%), and if monitoring with $ETCO_2$ was used, specialist teams were more likely to obtain a blood gas sample before departure (74 vs. 0 %).

2.3.6 Use of a standardized patient care handoff

Patient handovers have been identified as safety risks by important health organizations. This has resulted in, for example, the Swedish Association of Local Authorities and Regions (SKL) having prepared a document (SBAR) for structured patient handover. [*Cited 2019 May 5]. Avaliable from https://skl.se/halsasjukvard/patientsakerhet/sbarstruktureradkommunikation.748.html*
A structured communication for patient handover is also important in inter-hospital transports since care providers change.

A local quality improvement project introduced a standardized transport handover process that included parental input. The primary measure was provider satisfaction. Improvements in provider perception of communication and overall satisfaction with patient handovers for patients transported by a specialized pediatric transport team and admitted both to general hospital wards and intensive care units was achieved.[61] Authors point out that sustainability of this approach in work is unknown secondary to limited follow-up.

2.4 Monitoring during pediatric inter-hospital transportation

Today specialized pediatric transport teams act as an extended arm from the tertiary PICU to referring hospitals. They provide best possible care for a wide variety of disorders and deliver PICU resources both in skilled personnel and special PICU equipment to the referring hospital.

The first prospective, randomized clinical trial in pediatric inter-facility transport was published in 2011.[62] It was designed to determine the impact of improved blood pressure monitoring during pediatric inter-hospital transport and the effect on clinical outcomes in patients with systemic inflammatory response syndrome (SIRS) and moderate-to-severe head trauma. 94 patients 1-17 years were included. Patients in the intervention group received more intravenous fluid, had a shorter hospital stay and had less organ dysfunction.

2.4.1 Near-infrared spectroscopy with special focus on its use in a transport environment

Monitoring of oxygenation is important to ensure patient safety and the best possible patient outcome. Near-infrared spectroscopy (NIRS) is a noninvasive method for monitoring regional tissue oxygen saturation (rSO_2).[63] NIRS uses light of 700-1000 nm wavelength, a spectrum which most biological tissues except for hemoglobin and cytochrome oxidase are rather transparent to, which allows for deep light penetration. A light emitting diode sends out the near-infrared light in an ellipse form to a detector, the photon penetrating depth in tissue is depending on the source-to-detector distance (mean depth is approximately 1/3 of source/detector distance),[64, 65] *Figure 1.*

Oxygenated (HbO_2) and deoxygenated (HbR) hemoglobin absorb near-infrared light at different wavelengths, differences in absorbance between

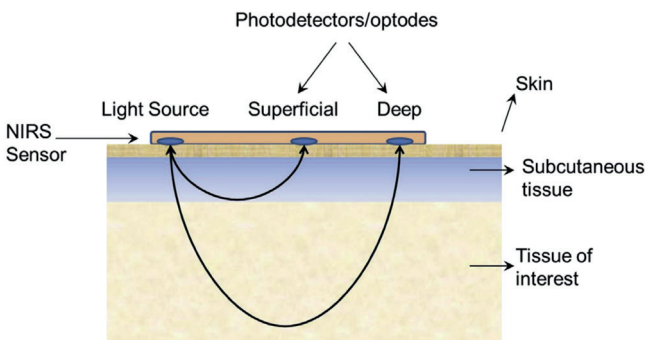

Figure 1.
A diode sends out near-infrared light which travels to either a proximal or distal detector. Superficial and deep optical signals are processed separately. Data from the superficial tissue is subtracted and suppressed, reflecting rSO_2 in deeper tissues. Downloaded from Google (wiki.library.ucsf.edu)

HbO_2 and HbR are detected by the sensor and the ratio between HbO_2 and HbR is expressed as the regional oxygen saturation (rSO_2) of the tissue. Since most blood in tissue is post arteriolar (approximately 3:1 venous to arterial blood) the rSO_2 is an estimate of regional venous saturation.[64, 66-68]

NIRS-monitoring is attractive in neonatal and pediatric practice not only because it is noninvasive, but also because the penetration of the signal into the tissue corresponds well with the anatomy of neonates, infants and children.[66] Pediatric studies have demonstrated good correlation between cerebral regional oxygen saturation and jugular venous bulb saturation.[69] Anterior abdominal (splanchnic) rSO_2 has shown strong correlation with gastric intra-mucosal pH as well as serum lactate and systemic venous oxygen saturation (SvO_2) in children with congenital heart disease (CHD).[70] In this group of patients with risk for low cardiac output, splanchnic rSO_2 correlated better with systemic markers of oxygenation and perfusion such as serum lactate and SvO_2 than did measurements over the renal bed. NIRS does not require a pulsatile flow for its measurements, which is considered advantageous in low-perfusion conditions and may help to identify patients at high risk for low cardiac output and adverse events.[67, 70-72] There is an inter-individual difference in NIRS values and therefore a trend monitoring approach has been recommended to minimize biological variation.[64] In neonates rSO_2 values change during the transition from fetal to extrauterine circulation and postnatal reference values at different ages have been published.[73, 74]

Areas of use for NIRS monitoring today are many, for example in pediatric and adult cardiac surgery (neuroprotection), in vascular surgery, in neonatal and pediatric intensive care and as a measure of the quality of cardiopulmonary resuscitation.[75] NIRS has also been found to detect a decrease in cerebral rSO_2 earlier than SpO_2 from pulse oximetry in children undergoing anesthesia with periods of apnea during airway laser surgery and has been reported to be effective in detecting postoperative apnea in neonates.[72, 76] In a review from 2014 authors concluded that despite the small single-center sample size and lack of randomization, recent studies have indicated a potential benefit in the utilization of NIRS in cardiac critical care.[71] Nevertheless, more confirmatory studies are required to determine whether NIRS can be utilized to improve outcome with goal directed therapy.[67, 71]

Increasing interest has been drawn to the use of NIRS monitoring in the pre-hospital area since it is non-invasive and fairly easy to use, for example as a tool to assess traumatic brain injuries as well as need for blood transfusions in trauma patients.[65, 77]

A systematic literature review was performed on NIRS methodology in December 2016, from the perspectives of NIRS-monitoring during transports in different vehicles. After inclusion and/or exclusion criteria had been considered five articles were finally selected for qualitative analysis.

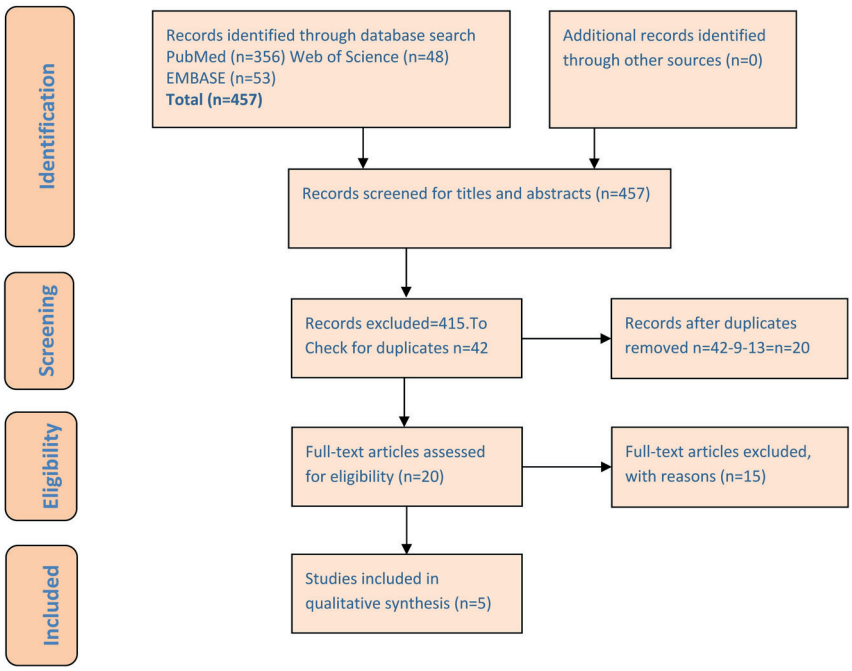

***Figure 2**. PRISMA-diagram (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) of the selection process. The selection and collection of articles for the review included four steps: Identification, screening, eligibility and inclusion.*

Burillo-Putze et al. reported in 2002 that the NIRS-monitor did not interfere with medical or aeronautical equipment.[78] They reported that the NIRS monitor had a 4-hour battery life. They found that rSO_2 remained relatively constant at each altitude (0-5000 feet) in healthy volunteers.

Kikukawa et al. reported in 2008 that NIRS provides a sensitive method for measurement of pre-frontal oxygen status e.g. pre-frontal oxy-hemoglobin concentration changes in helicopter pilots as a method for monitoring of cognitive demand during flight.[79] The effects of vibration in the helicopter had no evident effect on the NIRS signals.

In 2012, Wheaterall et al. who studied a NIRS monitoring system with availability of absolute oximetry monitoring, allowing reading without initial baseline calibration, found that 50% of NIRS-monitors were unable to provide monitoring outdoors without extra covering of the sensor, due to

ambient light exposure.[80] Inside ground ambulances 100% of applied sensors provided monitoring, but interruptions resulting in loss of monitoring time were found in 6% of sensors. In helicopter transports, the sensor closest to the window provided successful monitoring more than 70% of the time in 86 % of transports compared to 100% of transports for the inboard sensor, the reason being ambient light. Another challenge identified by the authors was NIRS-monitor battery power loss which abbreviated monitoring time. There was no signal loss due to patient movement or vehicle vibration. They found the screen display visibility to be reduced in very bright direct sunlight, but otherwise acceptable.

Stroud et al. found that cerebral oxygen saturation in pediatric patients transported by helicopter may change with acute changes in altitude, especially in patients with respiratory illness and in need of high levels of respiratory support and at altitudes above 5000 feet.[81] They concluded that cerebral oxygen saturation monitoring with NIRS may be a useful monitoring tool during inter-hospital helicopter transports of pediatric patients.

In their study from 2016, Valente et al. reported a decrease of at least 20% in cerebral rSO_2 in 50% of study patients (pediatric and neonatal patients) during transport in ground ambulance, helicopter and fixed wing aircraft, but without any clinical deterioration, and therefore no interventions occurred.[82] In the same study there was no significant association between patient positioning in transport vehicle and decreased cerebral oxygen saturation during take-off or landing.

All studies had methodological shortcomings and the area most affected was the risk of selection bias. All studies also had a small sample size. Another shortcoming was the lack of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals) which were not reported in any of the studies for the index test and only presented for the reference test in one study.

Furthermore, there was great heterogeneity among NIRS-monitors that were used in the different studies. In the two studies with pediatric patients the same type of monitor was used (INVOS 5100C). This monitor is still manufactured and in clinical use unlike its precursor the INVOS 4100C which no longer is in clinical use but was studied in the article from 2002.[78]

Generally, NIRS is widely used in different clinical settings, but like most medical technology it has not been developed for the pre-hospital environment with its special requirements on patient and vehicle movements or vibrations, the absence of medical equipment's interference with flight instruments and vice versa, the influence of ambient light exposure, the duration of

battery life and weight of equipment to mention some.

All five studies concluded that cerebral oxygen saturation monitoring with NIRS can be used in a patient transport environment. They also stated that NIRS may be a useful additional monitoring tool to already existing medical monitoring equipment during inter-hospital transports, but that larger sample sizes are needed and preferably also studies designed to guide therapeutic interventions.

According to the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU)[83] there are 4 steps in the evaluation of diagnostic tests, with the last step being the question if outcome is better for patients undergoing the test compared with similar patients who did not undergo the test. This review showed that the research in this area cannot yet give an answer to that question.

Searching the literature for NIRS utilization in a transport environment also showed that measurements in previous studies had been carried out by punctual monitor readings by the transferring personnel. There was no description of the electronically stored data being examined in an attempt to validate the method in a transport environment. Fairly few articles were found and only two concerned pediatric patients, meaning that the number of children examined is small; 17 patients transported by helicopter[81] and 24 patients, of which 5 were transported in fixed wing aircraft, in the study by Valente et al.[82]

2.5 Severity of illness scoring systems in pediatric transport

There is no validated, scoring system for evaluation of physiologic stability and risk assessment in relation to pediatric inter-hospital transports. Therefore, several scoring systems appear in the pediatric transport research literature. For neonatal patients, two similar objective scoring systems have been validated for transport assessment.[84-86]

In order to evaluate the effect of the retrieval process on the validity of three common scores: pre-ICU PRISM, PRISM and PIM, a study was performed in 2002.[87] The conclusion was that PIM appeared to offer advantages over the other two scores in terms of being less affected by the retrieval process and easier to collect, but that a recalibration of all scoring systems was needed. Since then the PIM score has been revised into PIM2[43] and PIM3.[88]

The Pediatric Index of Mortality (PIM2) score has been validated in the pediatric critical care population to predict mortality based on data collected within the first hour of admission to a PICU.[42, 43] PIM2 describes how ill the

child was at the time when intensive care started. The observations to be recorded are those made at the time of first face-to-face (not telephone) contact between the patient and a physician from PICU, or a physician from a specialist pediatric transport team. PIM2 captures data of each variable measured from point of first contact until one hour post PICU admission. The first contact may be on retrieval.[43] PIM2 was used in a large study involving specialized pediatric transport teams in England and Wales.[23]

The Pediatric Risk of Mortality (PRISM) score has been frequently used in studies as a tool to assess the outcome of transported, critically ill children and as an indicator of the effectiveness of a specialized pediatric transport team on outcome.[15, 18, 22, 89, 90] The use of pre-transport PRISM to estimate the requirements for intensive care or major interventions during transport has been discouraged since it may underestimate these needs.[91]

The Transport Risk Assessment in Pediatrics (TRAP) score's ability to contribute in appropriate placement for referred pediatric patients was evaluated in a feasibility study.[92] A high score was significantly associated with PICU admission lasting >24 hours. In a study from 2001, pediatric illness severity was measured using physiological pre-transport variables; only four variables could reasonably predict in-hospital mortality: systolic blood pressure, respiratory rate, oxygen requirement, and altered mental status.[93] This study also showed that as risk of mortality based on pre-transport variables increased, the incidence of major patient interventions performed by the referring hospital and transport team also increased as well as the occurrence of unplanned events during transport.

A Modified Pediatric Early Warning Score (PEWS) to assess stability of pediatric patients before, during and upon arrival at the receiving hospital, was studied in 2012 in an effort to consistently assess patient acuity and the impact of the transport team's interventions.[94] Authors argue that a tool which would facilitate clear communication between referring and receiving hospital may allow for more appropriate team composition and mode of transport.

In a retrospective study from 2014 the PIM2 scores collected at three different timeframes in children transported to PICU by a specialized pediatric transport team were similar.[95] Authors concluded that they did not find evidence that different sets of rules were required for PIM2 data collection in transported and direct PICU admissions.

3 AIMS

The overall aim of this thesis was to evaluate the impact of inter-hospital transport on seriously ill children with special reference to short and long-term outcomes and the effects of altitude.
The specific aims were:

- To compare outcomes and resource use in children acutely admitted to PICU after transport with a specialized pediatric transport team to children acutely admitted through other sources
- To study short and long-term outcomes in children, acutely transported to PICU by a specialized pediatric transport team, in relation to age and risk score at admission. The hypothesis was that neonatal patients would be more resource demanding and have higher mortality rates than older patients
- To evaluate the need for an arterial blood gas in calculation of Pediatric Index of Mortality 2 (PIM2) and Predicted Death Rate (PDR) risk score
- To investigate the applicability of NIRS data electronically stored during transport in fixed wing air ambulance
- To examine the effects of high altitude on regional oxygen saturation during fixed wing air ambulance transports of critically ill children.

4 MATERIAL AND METHODS

4.1 Ethical considerations

This thesis was conducted according to the Helsinki Declaration (World Medical Association (WMA) Ethical Principles for Medical Research Involving Human Subjects 1964.[96] All studies were performed after approval from the Stockholm Regional Ethical Review Board.[97] In Study III The Stockholm Regional Ethical Review Board approved a nationwide study after consulting with the regional boards in Gothenburg and Lund (Dnr 02-483). For this cohort, extended ethical approvals were sought and subsequently granted (Dnr 2007/1073-32, Dnr 2008/39-32, KI-Dnr 2009/1295-32, KI-Dnr 2016/2274-32).

Studies I-III are registry studies, the data contained no protected health information and there were no changes in patient care due to the database entry, which meant that the need for informed patient consent was waived. All data were presented at group level.

In Study IV and Study V, participation has been voluntary, informed consent obtained and all participants have been guaranteed full confidentiality.[98, 99]

This research project concerns children, and participating children have been critically ill and have therefore not been able to receive either oral or written information. Special care has therefore been taken to ensure that the children's guardians have understood the information given and that they did not feel obliged to participate in this project.[99, 100]

4.2 Overview of methods

Study	Design	Study population	Number of participants	Statistical methods
I	Retrospective register study	Children 0-18 years, acutely transported to PICU 2008-2013 by PETS	221 In control group: 3665 patients	Chi-square statistics with Yate´s correction. Mann–Whitney U-test. Kaplan-Meier method
II	Retrospective register study	Children 0-18 years, acutely transported to PICU 2008-2016 by PETS	401	Chi-square statistics with Yate's correction. Mann–Whitney U-test. Kaplan-Meier method. ROC analysis with Youden index
III	Retrospective cohort	Children 0-16 years, consecutive admissions to PICU in Gothenburg 2008-2010	990	Fisher's exact test. Spearman ranking for evaluation of correlations. Mann–Whitney U-test.
IV	Methodological study	Children 0-15 years scheduled for air ambulance transport 2014-2016	38	Friedman's test with Dunn's multiple comparison. Ansari–Bradley test. Smoothing by the Savitzky–Golay filtering method.
V	Prospective observational study	Children 0-15 years scheduled for air ambulance transport 2014-2019	39	Kruskal-Wallis statistics with Dunn's multiple comparison test. Friedman's test with Dunn's multiple comparison tests. Wilcoxon signed-rank test was used for the comparison of column medians to a hypothetical value.

Table 1. An overview of the study methods.

4.3 Study descriptions

4.3.1 Study I-II

4.3.1.1 Patient population

Study I: 221 consecutive acute admissions (age 0-18 years) to PICU at Astrid Lindgren Children's Hospital after an acute inter-hospital transport by a specialized pediatric transport team. The study population was compared to a cohort of consecutive acute admissions (n=3665) to the same PICU through other routes.

Study II: 401 consecutive acute admissions (age 0-18 years) to PICU at

Astrid Lindgren Children's Hospital after an acute inter-hospital transport by a specialized pediatric transport team.

4.3.1.2 Cohort design

All patients, between 0-18 years of age, acutely transported to the PICU at Astrid Lindgren Children's Hospital by the department's specialized transport team 1 January 2008 - 31 December 2013 were retrospectively enrolled. In Study I a control group of all other acutely admitted PICU-patients during the same time period but through other routes was also created. The two groups were compared regarding background data, length-of-stay (LOS) in PICU, Predicted Death Rate (PDR), PICU-mortality and 30-day mortality. Markers of resource use in PICU that were extracted were: invasive ventilation, length of ventilation and PICU specific therapies such as vasoactive support, inhaled nitric oxide and continuous renal replacement therapy (CRRT).

An extended data collection was done including acutely transported patients to the PICU at Astrid Lindgren Children's Hospital by the department's specialized transport team during 1 January 2014 – 31 December 2016. This larger cohort 1 January 2008 – 31 December 2016 formed Study II.

4.3.1.3 Data source and collection

Data from a Patient Data Management System (PDMS) where all patients admitted to the PICU at Astrid Lindgren Children's Hospital are registered was used. Transported patients were identified through the transport unit's transport register by unique personal identification numbers that follows each Swedish citizen from birth to death.

Admission data, consisting of admission and discharge dates, including the Paediatric Index of Mortality2 (PIM2) score and its derived PDR, LOS and PICU diagnosis were collected in PDMS. Data is automatically collected from medical bedside devices into PDMS. Hence, information on ventilatory support including ventilatory days and PICU specific therapies could be collected from PDMS.

All patients are given a PICU diagnosis based on the primary reason for PICU admission. This data, which is based on the International Classification of Diseases version 10, Swedish Edition (ICD-10-SE) was also collected from PDMS and entered into the study database. Patients were grouped according to the different diagnostic groups.

In Study II, the study cohort was divided into subgroups based on patient age and PDR at admission.

The latest version of the Paediatric Index of Mortality (PIM3) was adopted

in Sweden in October 2016, patients transported October - December 2016, had their PIM3 recalculated to PIM2. Recalculations were done in a separate excel PIM2-calculator and checked by using a free online PIM2 calculator from SFAR – Société Française d'Anesthésie et de Réanimation *[Cited 2017 April 15] (https://sfar.org/scores2/pim22.php).*

4.3.1.4 Data quality assurance

All data from PDMS was received in electronic form and converted into an Excel spreadsheet (Microsoft Excel 2010). All entered data were both manually and electronically checked for errors. Erroneously included admissions (age>18, date of birth inconsistent with date of admission) were excluded. Temporary identification numbers were identified in the hospital charts for information of their date of birth, which was then entered into the study database. If no valid personal identification number was found, patients were excluded in Study II, since they could not be followed up in the national data base.

Dates for PICU admission and discharge were collected. Patients with a LOS in PICU less than one hour were manually checked in the hospital charts for admission time and discharge. If incorrect, the correct time was then entered into the database. After the last corrected admission, an additional number of ten admissions were checked. When ten admissions in a row showed consistent with data in hospital charts, the control was stopped. Patients with the longest LOS were checked against hospital charts in the same way, and correct admission and discharge time was entered into the database. After the last correction an additional number of ten admissions were checked. When ten admissions in a row showed consistent with data in hospital charts, the control was stopped.

All patients with PIM2 data recorded as systolic blood pressure = 0, as an indicator of cardiac arrest, were double checked in hospital charts and corrected and PIM2 recalculated if not found to be correct. This was also done for patients where pupillary reaction to bright light was recorded = No.

4.3.1.5 Data from national registers

The 30-day mortality data was provided through the Swedish Intensive Care Register. The long-term mortality rate for the transported group was obtained from the population registry (Swedish Tax Agency), by the unique personal identification numbers.

4.3.1.6 Long-term mortality calculations (Study II)

Long-term mortality was calculated using the last registered admission to PICU during the study period. Mortality calculations were done using the

Kaplan-Meier method (Study I and II), and patients were grouped both according to age and PDR at admission. A 30-day cut-off was used to define late death. To describe long-term mortality, we calculated conditional survival, defined as observed survival if the patient survived the first 30 days after admission to PICU. The reliability for predicting PICU, 30-day and 90-day mortality with PIM2 was tested by calibration of ROC curves at these time intervals.

4.3.2 Study III

4.3.2.1 Patient population

1793 consecutive admissions (1255 patients) aged 0-16 years. An arterial blood-gas sample was found in 990 admissions who then formed the study group.

4.3.2.2 Cohort design

This was a subset of data from a national prospective study from 3 PICUs in Sweden.[101] Patients 0-16 years, consecutively admitted to the PICU at Queen Silvia Children's Hospital, Gothenburg, Sweden 1 January 2008 – 31 December 2010 were enrolled. All admissions were grouped according to Australian New Zealand Paediatric Intensive Care (ANZPIC) registry. Patients with an arterial blood gas sample present at admission, regardless of diagnostic group, formed the study group. Two separate cohorts were identified based on PICU admission diagnosis. One with an admission diagnosis "Respiratory" and one called "Non-respiratory" with all other admissions.

4.3.2.3 Data collection

PIM2 and its derived PDR were recalculated in patients with an available arterial blood gas sample at admission, omitting the PaO_2/FiO_2 ratio, and the risk scores with and without the PaO_2/FiO_2 ratio present were thereafter compared. The difference in predictability between the respiratory and non-respiratory groups was compared with the PaO_2/FiO_2 ratio omitted from the PIM2 calculation.

4.3.3 Study IV and V

4.3.3.1 Patient population

Study IV: 38 pediatric patients, age range newborn - 4 years, scheduled for inter-hospital air ambulance transport were enrolled by convenience sampling.

Study V: 39 pediatric patients, age range newborn - 4 years, median age 12 days, who were scheduled for inter-hospital air ambulance transport were enrolled by convenience sampling.

4.3.3.2 Study design

The study population consisted of 38 (39 patients in Study V) seriously ill pediatric patients scheduled for inter-hospital transport in air ambulance between January 2014 and September 2016, convenience sampling (until January 2019 in Study V). Monitoring began at the referring hospital and ended at the receiving hospital. Patients were transported in Beech Super King Air 200 or Cessna Citation II 550 air ambulances.

Figure 3. *Interior photo from the air ambulance during Study V. The PhD student is keeping track of the study protocol. The study patient is mechanically ventilated.*

4.3.3.3 Equipment and procedures

Near-infrared spectroscopy (NIRS) with INVOS-5100C (Covidien, Mansfield, MA, USA) was used to monitor regional oxygen saturation (rSO_2). In all patients a cerebral (rSO_2-C) and an abdominal (rSO_2-A) NIRS sensor were applied, *Figure 4*. The probes had two light paths with an emitter/diode spacing of 30-40 mm and a light penetrating depth of 20-40 mm.

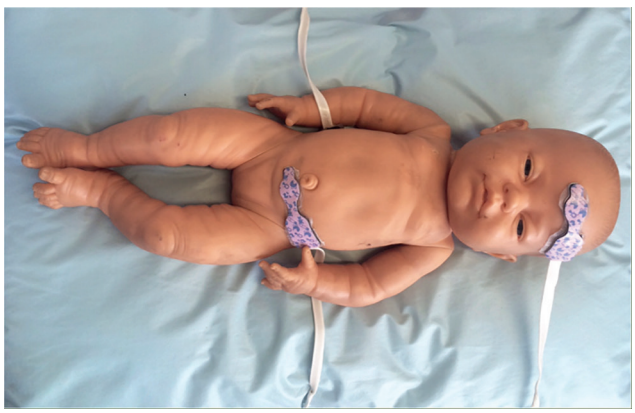

Figure 4*. Locations of cerebral and splanchnic sensors. Down loaded from Google, https://www.spiedigitallibrary.org/journals/journal-of-biomedical-optics/volume-21/issue-09/091306/Review-of-splanchnic-oximetry-in-clinical-medicine/10.1117/1.JBO.21.9.091306.full*

All patients were also monitored with standard hemodynamic monitoring, pulse oximetry, body temperature, respiratory rate and evaluation of level of sedation by Comfort-B.[102] Recorded values were noted in the study protocol before flight (base-line), during flight with cabin pressurization corresponding to ≥ 5000 feet and after flight. No clinical care decisions based on values presented on the INVOS monitor were allowed.

rSO_2 data were electronically stored by the INVOS monitor during transport and extracted and analyzed off-line. Data were downloaded to MS Excel 2010. For each patient zero values and unreliable values, meaning values which remained steady at a detection level of 15% ("floor-effect") were identified for both sensors during the entire monitoring sequence and removed before noise reduction of the signal.

In Study IV the Savitzky–Golay algorithm of smoothing and differentiation of data by simplified least square procedures (least-square fitting) was applied to the unprocessed signal data to perform noise reduction.[103] The 2nd order of smoothing polynomial in combination with the optimal number of neighboring points were determined to eliminate noise without detailed information being erased. MATLAB®, MathWorks (Natick, MA, USA) was applied for the implementation and analysis of the Savitzky–Golay filters.

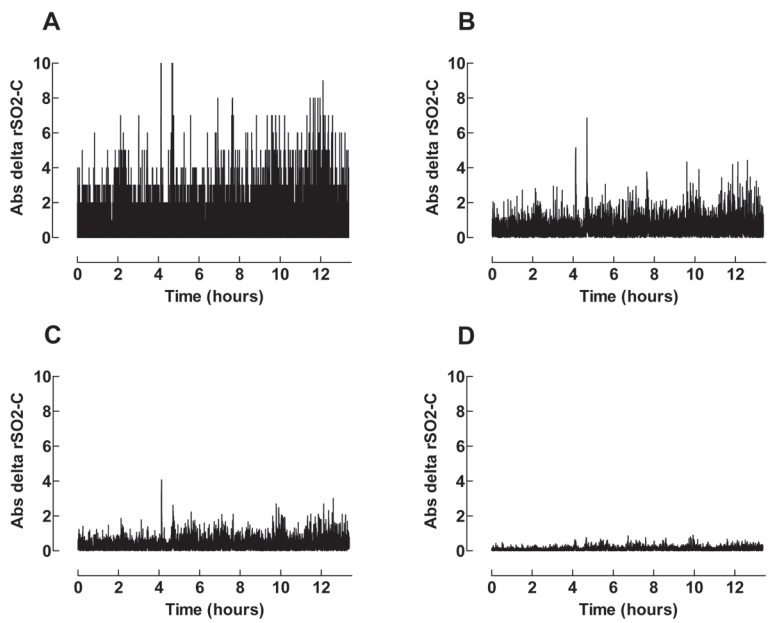

Figure 5. *The variability in the signal was investigated by using the absolute difference between 2 adjacent readings. 5A: Unprocessed data, 5B: 3 neighbors, 5C: 5 neighbors and 5D: 20 neighbors.*

The principle of signal smoothing:[104]

1) A data interval is selected
2) A low-order polynomial function is fitted to the data within this interval
3) The experimental point is replaced by the polynomial predicted one at the center of the interval
4) The process is repeated after shifting the window ahead by one sampling interval

In Study V a cerebral - splanchnic ratio (rSO_2-C/rSO_2-A) for each patient at baseline and at altitude ≥ 5000 feet was calculated to further evaluate differences between cerebral and splanchnic oxygenation.

4.4 Statistical analysis

4.4.1 All studies

Continuous data are reported as medians and interquartile range (IQR). Categorial data are expressed as median (range) or frequencies (proportions). A p-value ≤ 0.05 was considered statistically significant and reported p-values were from two-sided tests. Statistical analyses were undertaken using MS Excel (Microsoft Corporation, Redmond, Washington, USA) and Graph-Pad prism 5.04 (GraphPad Software Inc., La Jolla, CA, USA).

4.4.2 Study I and II

Survival was depicted by the Kaplan-Meier method. Classified data from two independent populations were compared using Chi-square statistics with Yate´s correction. Two independent groups of samples were compared using the Mann-Whitney U-test. SMR and its 95% confidence intervals were calculated as given by Liddell.[105] The maximum effectiveness of PDR was evaluated by ROC analysis with Youden index in Study II.[106]

4.4.3 Study III

Correlations were assessed by the Spearman rank correlation test. Two independent groups of samples were compared using the Mann-Whitney U-test. Classified data from two independent populations were compared by Fisher's exact test. SMR and its 95% confidence intervals were calculated as given by Liddell.[105] Bias was calculated as outlined by Sheiner and Beal.[107] The variance ratio test was used for the comparison of the variability of data in two populations.

4.4.4 Study IV

Several dependent populations were compared with Friedman's test with Dunn's post-test. The equality of scatter in two populations was performed by the Ansari–Bradley test. The NIRS curves were smoothed by the Savitzky–Golay filtering method.[103]

4.4.5 Study V

Several independent populations were compared with Kruskal-Wallis statistics with Dunn's post-test. Coefficient of variation was compared with the Friedman's test with Dunn's post-test. The Wilcoxon signed-rank test was used for the comparison of column medians to a hypothetical value.

5 SUMMARY OF RESULTS

Only main results are presented. For detailed results, please see the full-text manuscripts enclosed at the end of this book.

5.1 Study I

In Study I we investigated outcomes of patients acutely transported to PICU by a specialized pediatric transport team. Transported patients were compared to a control group of children acutely admitted to the same PICU over the same 6-year period but through other routes. Transport distance, mode of transport and diagnoses in relation to mortality were also studied. The main findings are presented in *Table 2*.

We found that transported children were younger, sicker, had a longer LOS in PICU and needed more of PICU specific therapies than other acute admissions. Transport itself, assuming an experienced and suitably equipped transport team, did not increase risk of death, which was evidenced by a similar Standardized Mortality Ratio (SMR) in both groups. We also found that long transport distances were not associated with a higher mortality risk.

An incidental finding of PICU mortality, even though not statistically significant, being especially high in neonates < 28 days, evoked the questions that led to Study II.

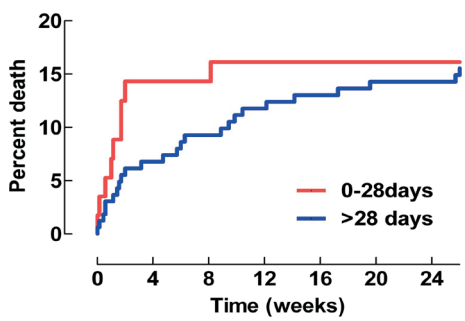

***Figure 6**. The survival curve indicates that the youngest patients in a larger proportion died earlier on, but over time the two curves seem to approach each other.*

Patient characteristics	Acutely Transported	Acutely admitted by other routes	p-value
No. of patients	N=221	N=3444	
Age, median (IQR)	0.40 years (0.08-1.59 years)	1.32 years (0.16-6.70 years)	< 0.0001
No. of patients ≤ 30 days	58 (26.2%)	667 (19.4%)	0.0164
No. of patients < 1 year	141 (63.8%)	1560 (45.3%)	0.0004
Diagnostic Group			
Respiratory	102 (46.1%)	901 (26.2%)	< 0.0001
Neurological including convulsions	11 (5.0%)	537 (15.6 %)	< 0.0001
Trauma and poison	10 (4.5%)	379 (11.0%)	0.0035
Infection including sepsis	19 (8.6%)	126 (3.7%)	0.0005
Malformations	25 (11.3 %)	367 (10.9%)	0.8465
Certain perinatal conditions	7 (3.2 %)	98 (2.8%)	0.9441
Resource use in PICU			
Mechanical ventilation	171 (77.4%)	1193 (34.6%)	< 0.0001
Duration of mechanical ventilation, median (IQR)	93.8h (41.5 – 201.8h)	44.5h (13.7 – 113.5h)	< 0.0001
Inhaled Nitric Oxide (iNO)	26 (11.8%)	103 (3.0%)	< 0.0001
Vasoactive drugs	54 (24.4%)	271 (7.9%)	< 0.0001
Renal replacement therapy (CRRT)	6 (2.7%)	49 (1.4%)	0.2127
Extracorporeal membrane oxygenation (ECMO)	13 (5.9%)	65 (1.9%)	0.0002
Time in PICU, median days (IQR)	4.24 (1.81 – 8.80 days)	1.06 (0.60 – 2.97 days)	< 0.0001
Patients outcome			
PDR, median (IQR)	5.58% (1.44 – 11.49)	1.39% (0.76 – 4.02)	< 0.0001
Expected mortality	24 (10.9%)	174 (5.0%)	0.0004
PICU mortality	15 (6.8%)	85 (2.5%)	0.0003
30-day mortality	19 (8.6%)	116 (3.4%)	< 0.0001
SMR (95 % CI)	0.618 (0.346 to 1.02)	0.489 (0.390 to 0.604)	0.2832

***Table 2**. Patient characteristics and outcomes for patients acutely transported by the specialized pediatric transport team and for patients acutely admitted through other routes to the PICU. Selected diagnoses are included in the table, for all diagnoses and characteristics please see the full-text manuscript.*

5.2 Study II

In Study II age-related differences regarding short-and long-term survival, PICU-LOS and resource use during transport and in PICU among transported patients were evaluated. We also investigated the impact of PIM2 and PDR at admission on survival.

Median follow-up time for the entire cohort was 3.4 years (IQR 1.7-6.3 years, range 0-10.2 years) and for survivors during the study period 4.4 years (IQR 2.3-6.7 years, range 0-10.2 years). The median PICU-LOS was 3.8 days and similar for all age groups. Mechanical ventilation was high during transport (71.9%) and in PICU (78.3%), there was no difference in use between age groups. Vasoactive support was used during 12.2% of all transports and in 25.2% of all PICU admissions. Inhaled nitric oxide (iNO) and Extra Corporal Membrane Oxygenation (ECMO) therapy were more common in neonatal transports, in other respects we found no difference between neonates and older children regarding resource use.

Immediate survival after PICU treatment was 91.6% in neonates, 92.3% in infants (>28 days-1 year), 97.2% in children >1-4 years and 94.4% in children >4 years. Of all PICU deaths, 61.5% occurred during the first week of PICU treatment.

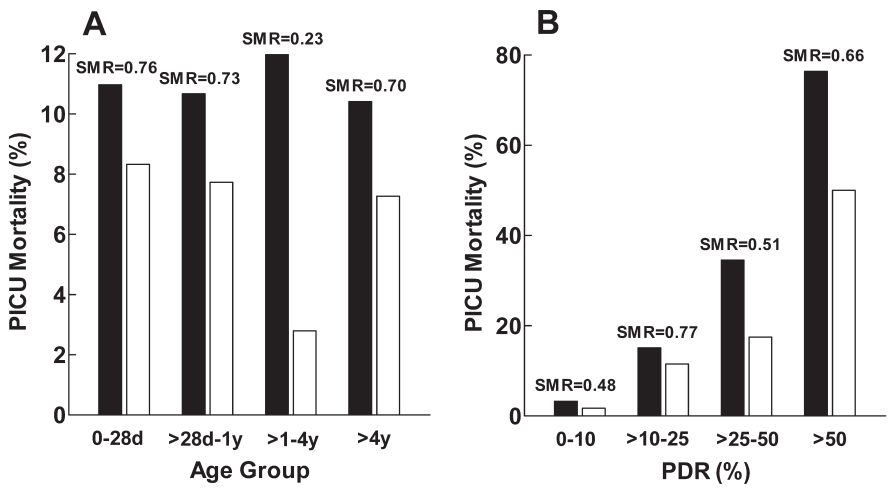

***Figure 7**. PICU mortality in relation to A: age at admission and B: PDR at admission. Observed PICU mortality was lower than expected for the entire cohort with a SMR of 0.59 (95%CI: 0.383-0.860) p<0.004.*
Black bar=Expected mortality, White bar=Observed mortality.

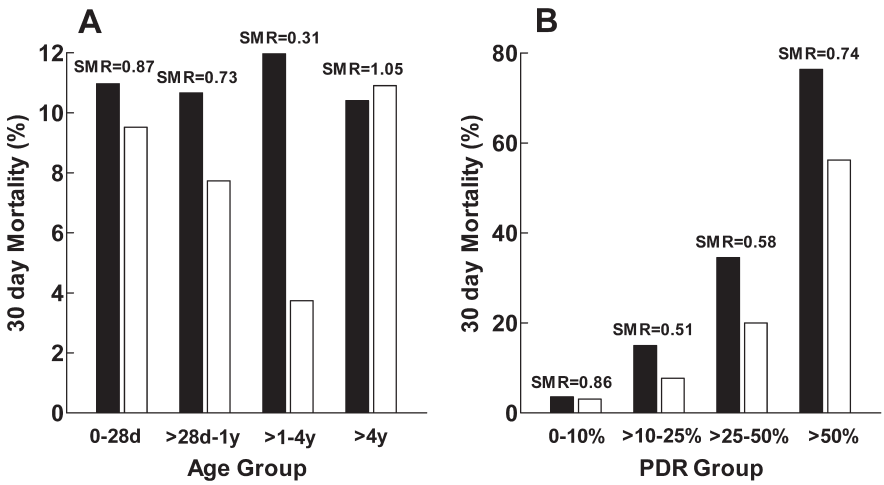

***Figure 8**. The 30-day mortality follow-up in relation to, A: age at admission and B: PDR at admission, showed a SMR of 0.68 (95%CI: 0.457-0.967) p<0.03 for the entire cohort. SMR in children > 4 years 1.05 (95%CI: 0.383-2.281), p=0.98. Black bar=Expected mortality, White bar=Observed mortality.*

Almost 70 % of late deaths occurred within the first year (54% within the first 6 months) and over 90% within the first three years. Of all deaths within the first year 47.8% were in infants (>28 days-1 year) and 34.8% of deaths occurred in the age group >1-4 years. In the neonatal group no deaths occurred after discharge from intensive care. Log-rank tests (Mantel-Cox) comparing Kaplan-Meier curves of long-term survival and age groups at admission showed no statistically significant difference.

When long-term mortality was investigated in relation to PDR, the majority, 63.6% of all late deaths occurred in PDR group 0-10% and over 60% of them died within the first year, 30% of deaths during the first year occurred in PDR-interval >10-25%. Thereafter no deaths occurred in this group during the study period. In PDR >50%, half of the group died at PICU and one more patient died within the first 30 days. Thereafter no additional deaths occurred in this group, which resulted in an overall survival of 43.7% and a conditional 5-year survival of 100%, *Table 3*.

Group	n	PICU survival, n (%)	30-day survival, n (%)	1-year survival, n (%)	5-year survival, n (%)	5-year conditional survival, %
0-28 days	84	77 (91.6)	76 (90.5)	74 (88.1)	74 (88.1)	97.4
>28 days-1 year	155	143 (92.3)	143 (92.3)	132 (85.2)	131 (84.5)	91.6
>1-4 years	107	104 (97.2)	103 (96.3)	95 (88.8)	91 (85.0)	88.3
>4 years	55	51 (94.4)	49 (89.1)	47 (85.4)	43 (78.2)	87.8
PDR 0-10%	293	288 (98.3)	284 (96.9)	271 (92.5)	263 (89.8)	92.6
PDR >10-25%	52	46 (88.5)	48 (92.3)	41 (78.8)	41 (78.8)	85.4
PDR >25-50%	40	33 (82.5)	32 (80.0)	29 (72.5)	28 (70.0)	87.5
PDR >50%	16	8 (50.0)	7 (43.7)	7 (43.7)	7 (43.7)	100

***Table 3**. Survival numbers for 4 different age categories and 4 different PDR categories after PICU treatment, 30-day mortality, 1-and 5 years later. Conditional survival = Observed survival if the patient survived the first 30 days after admission to PICU.*

There was a high mortality rate in patients with multiple transports, 36% of these patients died during the study period, a majority of those deceased died outside PICU.

5.3 Study III

The influence of arterial blood gas (ABG) data (i.e. the PaO_2/FiO_2 ratio) on the estimation of the PIM2 score and the Probability of death (%) was investigated in Study III. 1793 consecutive admissions (1255 patients) aged 0-16 years were enrolled. An ABG was found in 990 admissions which then formed the study group. Patients were grouped as respiratory and non-respiratory as an attempt to investigate any important differences in relation to diagnoses.

In the non-respiratory group, there was close agreement between predicted and true Probability of death (%) even though the PaO_2/FiO_2 data was omitted. For the respiratory group, important deviations of the predicted Probability (%) from the true Probability (%) occurred for PIM2 score exceeding –2.20 (Probability of death > 10%). The difference in Probability (%) estimated from PIM2 with and without PaO_2/FiO was significantly larger in the respiratory group than in the non-respiratory group ($p<0.0001$), *Figure 9.*

In patients with Probability >10%, estimated without PaO_2/FiO_2 data,

the differences in Probability (%) with and without PaO_2/FiO_2 data were 3.161 (median value; IQR: 1.477 to 6.459) units in the non-respiratory group and 4.397 (median value; IQR: 2.802 to 9.251) in the respiratory group, respectively. The variability in the respiratory group was significantly larger ($p<0.0001$). The SMR was slightly, albeit not statistically significantly overestimated, by not including PaO_2/FiO_2 data in the calculation of the PIM2 score.

Patients with the PaO_2/FiO_2 ratio available had a statistically significant higher Probability (%) than patients without the PaO_2/FiO_2 ratio available at admission, 1.388% (0.8361–4.049) and 0.7509% (0.4064–2.179) respectively, $p < 0.0001$.

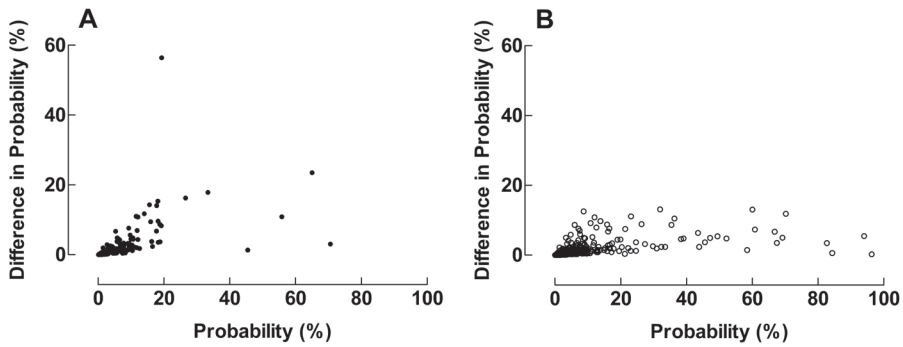

Figure 9. Difference in the Probability of death (%) with and without arterial blood gas data between A: respiratory and B: non-respiratory groups versus Probability (%) without arterial blood gas data.

5.4 Study IV

The collected data during transport were downloaded after the transport and cleared for artefacts, by removal of "zero-values" and "floor-effect" values, defined as values which remained steady at the lowest noted detection level of 15%, and thereafter smoothened by a noise-reduction algorithm. The Savitzky-Golay filtering technique, using smoothing and differentiation of the signal by least square procedures was applied on the NIRS-signal to reduce signal interference and thereby increase the ability to distinguish between real and artefact-related events. The 2nd order of smoothing polynomial in combination with the optimal number of neighboring points was determined to eliminate noise without loss of detailed information.

The signal noise decreased drastically when the numbers of neighbors was increased up to values of 20. A further increase only seemed to affect the noise level to a minor extent. However, visual inspection of the NIRS signal, after the Savitzky-Golay smoothing, showed that a further increase of the

number of neighbors beyond 20 still implied a considerable improvement of the signal, *Figure 10*. Tests revealed that fewer neighbors must be used when the study time frame was shortened. Significant distortions and loss of features of the data such as peaks and width were seen when the signal was smoothed with too many neighbours. Too few neighbors resulted in signals with too much noise.

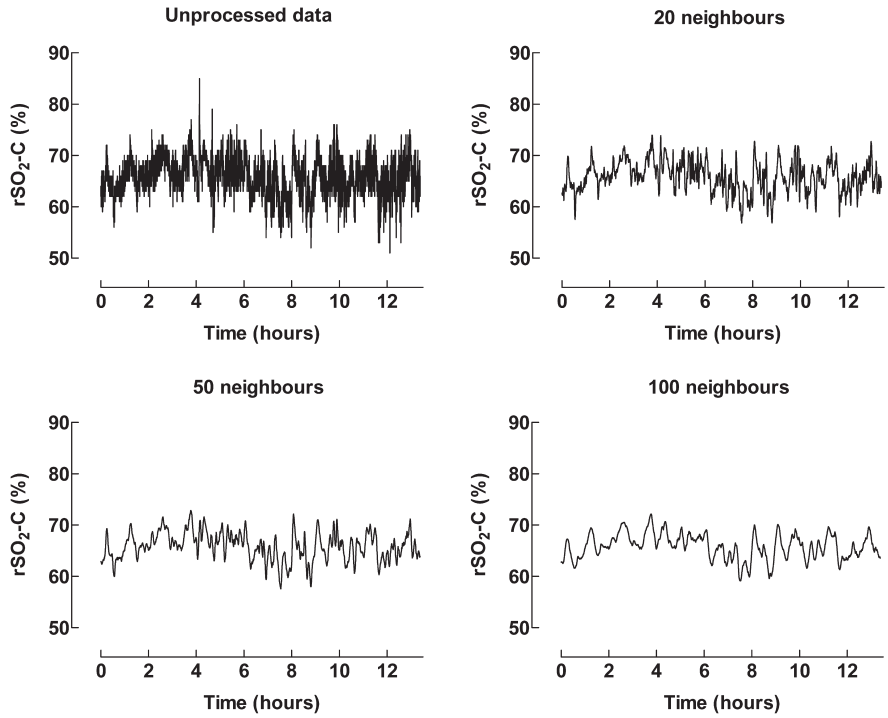

***Figure 10**. The unprocessed data as well as the effect of smoothing with 20, 50 and 100 neighbors respectively are presented with a total time frame of 13.5 hours. There were still details in the signal when 100 neighbors were used, but much less noise. The unprocessed data in the shown example consisted of more than 8000 readings.*

5.5 Study V

We compared regional oxygen saturation in cerebral and splanchnic tissue in this cohort of 39 patients and investigated if a relative change could be detected at ≥ 5000 feet as an effect of altitude. A ratio ≥ 1 was seen in a majority of patients (67%) at baseline and in even more patients (77%) at altitude ≥ 5000 feet. In 25 patients (64%) the rSO_2-C/rSO_2-A ratio was greater at altitude ≥ 5000 feet than at baseline. A statistically significant difference between rSO_2-C/rSO_2-A at baseline and at altitude was found in 36 subjects (92.3% of patients).

Among patients with a ratio < 1 at baseline, all but 2 had an increased ratio closer to 1 at altitude ≥ 5000 feet. We found no association between age, breathing support or diagnosis in patients with a ratio < 1.

In patients with cyanotic heart malformations the rSO_2-C value at altitude ≥ 5000 feet decreased compared to baseline in 6 of 9 patients and rSO_2-A decreased in 4 patients. In the subgroup of cyanotic patients 78% had a rSO_2-A value < 60% at baseline compared to only 30% of non-cyanotic patients. Different patterns of reacting to altitude was visualized by data smoothing, *Figure 11*.

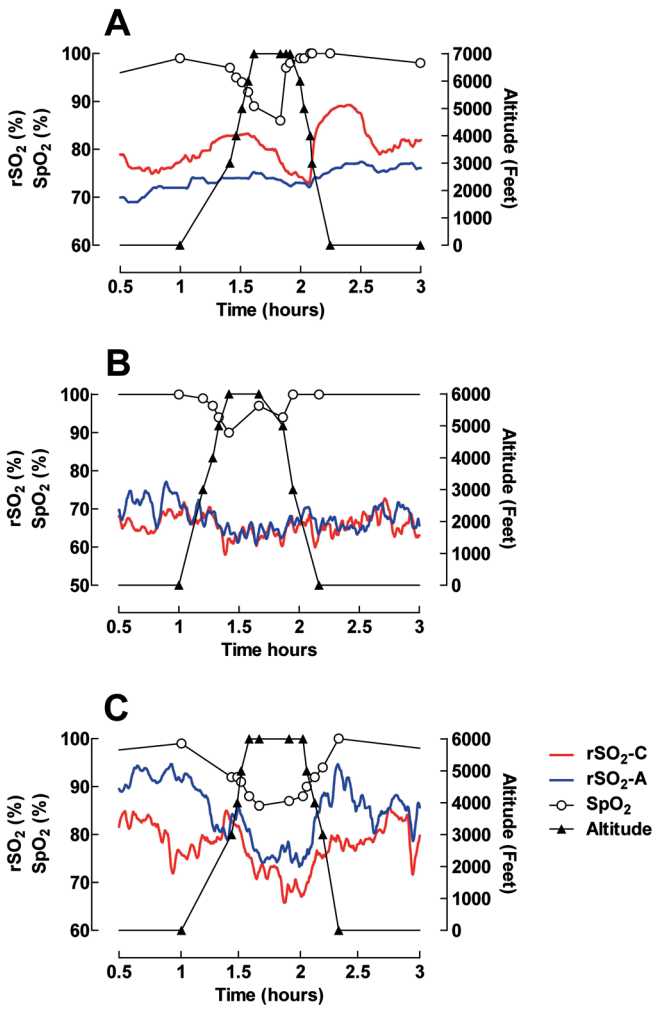

Figure 11. *Different patterns of reacting to altitude in three different patients. rSO_2-C was higher, at the same level and lower than rSO_2-A. The rSO_2 curves were smoothed with the Savitzky–Golay filtering method (20 neighbors were used).*

6 DISCUSSION

6.1 Summary of main findings

In this thesis we show that inter-hospital transport of seriously ill children, provided that the transport team is skilled and suitably resourced, does not increase the risk of death irrespective of transport distance. Moreover, we found that there was no difference in outcomes by age-groups at admission, specifically neonates versus non-neonates, as hypothesized. On the other hand, patients with multiple transports had a worse long-term outcome than patients transported once. We found that arterial blood gas analysis should be performed in PICU patients with a respiratory diagnosis where a high illness severity is suspected, or if otherwise considered clinically appropriate. Furthermore, that arterial blood gas analysis can be omitted in other patients without loss of accuracy of the PIM2 and Probability of death (%) score. We have demonstrated that the Savitzky–Golay filtering technique constitutes a feasible way to facilitate interpretation of changes in the near-infrared spectroscopy (NIRS) signal, and thereby regional oxygen saturation, in relation to physiological changes in patients and events during transport. Thus, when using the technique during air-ambulance transports, a decrease in cerebral and splanchnic oxygen saturation at altitude ≥ 5000 feet was observed, where cerebral oxygen saturation was preserved more than splanchnic oxygen saturation in most patients.

6.1.1 Study I and II

In more detail, we have performed the first study on pediatric critical care transports in Sweden, reporting outcomes of transported children admitted to a Swedish PICU (Study I). We found a higher predicted death rate (5.58% vs 1.39%), 30-day mortality rate (8.6% vs 3.4%), longer LOS (4.24 vs 1.06 days) and increased use of PICU specific therapies in transported children. Nevertheless, SMR was similar in the two groups. All retrievals were led by a pediatric intensive care consultant, since this is our routine, a team model which is less common for example in the US even for specialized pediatric transport teams.[108, 109] In 2015 Swedish professional societies agreed on a national referral strategy stating that critically ill children < 3 years should be transferred to a PICU.[10] In the same manner it was stated that transports of criti-

cally ill children < 3 years from general ICUs to PICU should be undertaken by teams where both the physician and the nurse are experienced in pediatric intensive care.

Even though studies similar to ours have previously been published from other regions of the world,[22, 23, 110] it was our conviction that the conditions of Swedish pediatric inter-hospital transports needed to be mapped. To be kept in mind is not only demographic differences, long geographic distances and challenging climate conditions, but also the rather sparse availability of pediatric intensive care beds in Sweden, which can be a limited resource especially during certain periods such as infection season.[1, 8, 9] In Sweden tertiary pediatric intensive care has been centralized to 4 centers and pediatric intensive care transports are growing by number. It is therefore important to ensure high quality of the service where specialized pediatric teams offer the most qualified method of transport, but also to find areas that need to be improved. Are the right patients being transferred? Are they being transferred in a safe way? Are their outcomes comparable to other PICU-patients?

Consequently, it is important that children who benefit most are transported to PICU. In Study I, we found that transported children were sicker, younger and stayed longer in PICU. In addition, the rate of respiratory failure was high with 77% mechanically ventilated admissions in the transported cohort, compared to 34.6% in the non-transported, in all indicating that the right patients were transported. We could also show that the transport per se does not increase the risk of death irrespective of transport distance.

In Study II we have presented some unique data that has not been reported previously, i.e. long-term survival outcome of acutely transported PICU admissions. The 4.4-year median follow up (range 0-10.2 years) for survivors is a significantly long period of follow up and provides a useful perspective on longer term outcomes of this cohort. The finding that patients transported multiple times have a worse long-term outcome has not been shown before. We found that cumulative mortality almost doubled within the first 6 months after PICU discharge, 6.5% vs 12.7% (n=26 at discharge, n=7 between PICU and 30 days and n=18 between 30-days and 6 months) and was 15.7% after 3 years. This is in line with previous reports where mortality appears to substantially increase after PICU discharge in a general pediatric intensive care population.[1, 101, 111] Survival over time is visualized by the Kaplan-Meier plot where the transported cohort is compared to the normal pediatric population in Sweden.

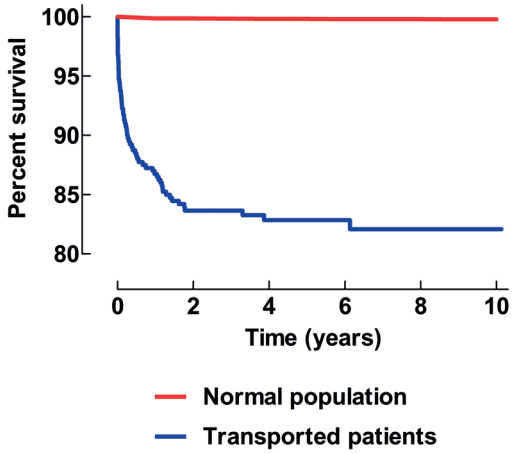

***Figure 12**. Comparison of survival over time in transported patients and in the normal pediatric population. Based on Statistics Sweden "Death rate per 1000 children in Sweden", SMR 114 (95% CI 86-151).*

Patients in our cohort showed both high short- and long-term mortality. Mechanical ventilation, number of ventilator days, use of vasoactive support and PICU LOS have been shown to be associated with poor long-term functional outcome.[111] These indicators of severity of illness were all comparatively high in our cohort as compared to other PICU patients (Study I). A potential association between inter-hospital transport from an intensive care area and PICU mortality has previously been shown, and a majority of patients in Study I and II were transferred from adult ICUs.[112] Our hypothesis that neonatal outcomes would be worse than for older children, was not proven correct. There was no mortality in this age group after ICU discharge, resulting in a conditional 5-year survival of 97.4%. Overall, medical vulnerability of transported children who survive critical illness in a PICU is significant. Therefore, assessing mortality at discharge from PICU alone must be challenged as it might not correctly present all consequences of critical illness in this cohort. The model of using the performance of PIM scoring in predicting 30 and 90-day mortality might be useful for this purpose.

6.1.2 Study III

In Study III we analyzed the impact of an arterial blood gas sample (i.e. the PaO_2/FiO_2 ratio) on the PIM2 and the derived probability of death in relation to diagnostic groups at admission. The rationale behind was an awareness that emerged when examining data from Study I, that is an arterial blood gas sample was missing in many of the PIM2 scores. Since PIM2 assumes a missing PaO_2/FiO_2 value to be 0 in the calculation of the score and nearly 50% of transported patients had a respiratory diagnosis and furthermore nearly 80% of all transported patients were mechanically ventilated we formulated the

research question. The problem with missing arterial blood gas sampling has been addressed by other investigators and the possibility to estimate PaO_2/FiO_2 from a SpO_2/FiO_2 value using a pulse oximeter instead of invasive arterial blood gas samples has been suggested.[113-118] Inaccuracy in pulse oximetry readings at saturations ≤ 85% has been reported, even suggesting that at saturations ≤ 85%, pulse oximetry alone should not be relied on in making clinical decisions.[119] Moreover, some authors have excluded SpO_2 values >97% in the pulse oximeter based estimates, since in this range large changes in PaO_2 result in minimal change in SpO_2[113, 114, 120] due to the oxygen dissociation curve. On the other hand, similar discrimination between pulse oximetry-based values and PaO_2/FiO_2 based values have been shown for PIM3 when all (SpO_2 0-100%) pulse oximetry values were used in a transport cohort.[116]

We found that PIM2 and probability of death was not altered when the PaO_2/FiO_2 was excluded from the logit equation, not for the entire study population nor for the non-respiratory group. Nonetheless, predictability was decreased for the respiratory group when probability of death was > 10%, if PaO_2/FiO_2 was omitted from the equation. There is no clear solution to the problem with the frequently missing PaO_2 values. However the results from this thesis suggest that it is not necessary to perform a blood gas sample in clinical practice since the PIM2 score mortality prediction is not limited, unless the child belongs to the respiratory group and a rather high severity of illness is suspected or if otherwise clinically indicated (circulatory monitoring, acid base-status, gas exchange etc.).

6.1.3 Study IV and V

During air transport the effects of altitude on patient oxygenation is of special importance. With increasing altitude, the barometric pressure will decrease and as a result also the partial pressure of oxygen. On air ambulance flights exceeding 2 hours in a pressurized cabin the cabin altitude corresponds to 7000 feet. Normal flying altitude (about 1-hour flight time), usually corresponds to 5000 feet inside the cabin. The current routine during transport is monitoring by pulse oximetry. This provides a continuous assessment of arterial oxygen saturation, but no estimate of tissue oxygen demand or an oxygen delivery imbalance, which could be of great interest especially in certain patient categories such as patients with cyanotic heart malformations or necrotizing enterocolitis.

Approximately 60 % of all transports performed by PETS are done by air-ambulance, among them are children transferred for open heart surgery.

As outlined in the Background section, the focus on NIRS utilization within the scope of this thesis has been on its use in a transport environment. Among the limitations with the NIRS technology mentioned earlier by others are technical issues such as different optical probes, sensors and algorithms in commercial devices which makes comparisons and reference values difficult.[74, 121, 122] Authors have also pointed out that noise reduction remains the most important factor in improving accuracy and precision of signal interpretation in vivo.[68]

When setting out to conduct Study V, we realized that NIRS real time readings were sometimes unreliable during transport and that individual values varied greatly, resulting in uncertainty. We therefore had to take a step back and find a way to improve the method before we could carry on with our study. We went back to analyze the electronically stored data and found that there was a great deal of artefacts (i.e. zero-values and "floor-effect" values) and noise in the signal. When making a literature search we understood that a particular method had been recognized by many for its ability to retrieve original signal structure while removing noise also in biomedical signal processing.[103, 104, 123-125] This algorithm has had a huge impact on the start of computer controlled analytical instruments, which was high-lightened when the scientific journal "Analytical Chemistry" in 2000 published an edition on the 10 most-cited papers from 1945 to 1999 and the original article written by Savitzky and Golay was one of them.[126]

We therefore introduced the Savitzky-Golay algorithm of smoothing and differentiation of data by simplified least square procedures (least-squares fitting) to perform noise reduction on the signal and thereby enable better signal evaluation, after the collected data had been cleared for artefacts. The second order of smoothing polynomial was used and the optimal number of neighboring points ("window-size") for the smoothing procedure was determined to avoid distortions of the signal. This resulted in a methodological study (Study IV) where we showed that by using this filtering method, we could perform noise reduction in the signal with very low signal distortion, which made it possible to relate signal changes to physiological events during transport. As an interesting finding in Study IV we observed that poor signal acquisition in the splanchnic sensor was most pronounced in children who had had previous abdominal surgery. The underlying reason is uncertain, possibly scarring of the subcutaneous tissue with inferior penetrating conditions for the near-infrared light can be responsible for this observation.

Study V is the first study to investigate regional tissue oxygen saturation with multisite registrations from both cerebral and splanchnic areas during

inter-hospital transport of critically ill children. In Study V we used the smoothing method to visualize different patterns of reacting to altitude in different patients. Both cerebral and splanchnic oxygen saturation decreased with statistical significance at altitude ≥ 5000 feet compared to baseline in a majority of patients and in most patients cerebral oxygen saturation was preserved more than splanchnic oxygen saturation. The clinical implication of this finding is unclear, however. Previous research has defined low rSO_2-C as a continuous decrease of > 20% from baseline.[65, 72, 76, 82, 127] We found this in only one patient, who also showed a simultaneous decrease in SpO_2. If the same decrease of > 20% from baseline was applied to rSO_2-A, using the information that rSO_2-A values in healthy newborns have been found to resemble rSO_2-C values by 48 h postnatal age,[73] we could observe this reduction in four patients, one without a simultaneous decrease in SpO_2. A more profound decrease in rSO_2-C and/or rSO_2-A than in SpO_2 was found in 5 patients, most obvious in rSO_2-A. On the other hand, a substantial decrease in SpO_2, without a corresponding decrease in rSO_2-C and rSO_2-A was found in 6 patients. We speculate that this might imply that cerebral tissue was protected by auto-regulation in this increasingly hypoxic environment and that splanchnic tissue was a leading indicator. Altogether we found that measurements of rSO_2-A involved more difficulties than rSO_2-C, but also gave more information in addition to measurements from pulse oximetry than did rSO_2-C. Ideally oxygen extraction would have been a more reliable measurement which could have provided additional information, but we were not able to extract continuous data from the pulse oximetry device, which limited this possibility. We believe that by combining regional oxygen saturation and the smoothing technique on line, NIRS has the possibility to become a useful technique to guide therapy to avert poor tissue-specific and global outcomes.

6.2 Methodological considerations

There are both strengths and limitations of the studies included in this thesis that might have interfered with results and interpretations.

A main limitation of both Study I and II is their retrospective nature as well as their lack of matched control groups.

Moreover, since the PIM2 score was collected from the first hour of PICU admission (rather than first contact with the transport team) it is possible that the PIM2 was inaccurate (physiology having been altered by interventions during transport) in both studies. The studies also evaluated outcomes for a single transport team and PICU, which is a limitation. A strength of

the studies is the linking of PICU data to a national registry to evaluate long-term survival, furthermore in both Study I and II consecutive patients were included, categorized by diagnoses set by the treating physician in the PICU and not by the researchers involved. In Study II patients were sorted by age or PDR at admission, the latter also scored by a PICU physician and data retrieved from PDMS. A possible selection bias could be the nature of the PICU being a tertiary center, where patients were transported for high-risk conditions such as intracranial bleeding accepted for neurosurgery, near-ECMO conditions or for continuous renal replacement therapy. In this perspective a case control study might have been a preferable method. No premature babies were included in any of the studies, nor patients transported to the neonatal intensive unit (NICU) since the PIM scoring system is not used in the NICU. Regarding Study II it might have been of additional value to divide the study group into two (2008-2013 and 2014-2016) to account for the effect of time on outcomes. It is likely that the reasons for death in the longer term are due to the chronic nature of the illnesses that the children may have had. A retrospective cohort analysis of 52,791 pediatric admissions to PICUs in the US stated that 53% of all admissions had a complex chronic condition. These children had a longer LOS and higher risk for PICU mortality than children without comorbidity.[128] Therefore, the absence of functional status prior to admission as well as data on chronic comorbidities is a weakness. In addition, we lack data on morbidity after discharge.

In the same manner, the design in Study III was retrospective with consecutive admissions to a single PICU. The cohort size in Study III was not based on statistical power calculations, a decision based on the aim of the study to investigate if the absence of a blood gas sample significantly affects the PIM2 value, i.e. the aim was not to perform analyses versus mortality where a considerable number of patients would have been needed. The coefficient for PaO_2/FiO_2 in the PIM2 equation contributes with only 0.2620 to be compared with an absent pupil reaction which contributes with a coefficient of 2.704 indicating the low weight of PaO_2/FiO_2 in the PIM2 calculation. The choice of a cohort with a high number of admissions (55%) with a recorded arterial blood gas sample was a strength. Previously reported percentages vary from 1.4 to 51.7% recorded PaO_2 values at admission.[88, 113, 115, 129] In the original article on the updated version PIM3, 44.2% of patients included had a recorded PaO_2 value.[88]

In Study IV and V a well-established and robust model for filtering technique was used, which should be considered to be advantageous. In both studies, data were evaluated and processed after the transport. Conclusions

on applicability of this method on line during the actual transport may therefore not be drawn in the scope of this thesis and should ideally be examined separately. Premature children were not included in any of the studies. Most children were neonatal patients with a median age of 9.5 and 12 days in the two studies, respectively. Consequently, a significant proportion of hemoglobin (Hb) in the blood would be fetal if the child had not been transfused with adult blood. In a study aimed to determine whether it is necessary to modify the coefficients used in NIRS calculations when fetal Hb is present it was shown that adult Hb coefficients can be applied to newborns, irrespective of the level of fetal Hb, without introducing a significant error.[130] In Study V a Hb measurement was not documented in 25% of patients at the time of transport, this could influence both rSO_2-C and rSO_2-A levels, but since each patient served as its own control, we think this effect is insignificant for the results. NIRS data were collected as continuous data which resulted in large numbers of data, while data from pulse oximetry on the other hand were collected as single values.

6.3 Clinical implications

Critically ill children can be transported, regardless of the distance, without increasing their risk of death provided that the team members are experienced in pediatric intensive care, and the equipment appropriate.

Transported children show a high mortality rate also after PICU discharge, especially during the first six months, and especially in children transported multiple times. Therefore, survival after transport should if possible be presented as survival after 90-days. In addition, the PIM score may be used in predicting 30-day and 90-day mortality, not only PICU mortality.

It is not necessary to have a blood gas sample just to fill in the PIM score. It should be taken when clinically indicated.

NIRS monitoring has potential benefit when cleared for artefacts and smoothened by a noise-reduction algorithm. It may serve as a complement to existing monitoring during inter-hospital air ambulance transport, especially in children with certain diagnoses such as cyanotic heart malformations.

7 CONCLUSIONS

Based on this thesis the conclusions are that:

- When transported by a specialized pediatric transport team critically ill children can be transferred, regardless of the distance, without increasing their risk of death. Despite a higher severity of illness and an increased use of PICU resources among transported children, the Standardized Mortality Ratio was similar to other acute admissions to PICU.
- A difference in survival among age-groups could not be demonstrated in transported patients, PICU resources such as iNO and ECMO were more common in the neonatal group. Overall, there was a significant mortality after PICU discharge which implies that survival to PICU discharge may not be the best measure of outcome for this group of patients.
- A PaO_2/FiO_2 value for the PIM score is needed only when the patient belongs to the respiratory group and a rather high severity of illness is expected.
- Reliable NIRS data can be obtained during transport when cleared for artefacts and smoothed by a noise-reduction algorithm.
- There was a decrease in both cerebral and splanchnic oxygen saturation as an effect of altitude, however cerebral oxygen saturation was better preserved than splanchnic. The clinical impact has still to be investigated, but NIRS has the potential to give insight into physiological processes during air-ambulance transports.

8 FUTURE PERSPECTIVES

- In this thesis we have found that transported children showed a continuous mortality risk after PICU discharge. In a future study it would be interesting to investigate the morbidity and functional status among transported patients, as well as all PICU patients in a longitudinal fashion after PICU discharge and correlate these findings to functional status including complex chronic conditions prior to transport/admission.
- In the future a national (or Scandinavian) multicenter study on outcomes in transported children would be both enlightening and educational, preferably in combination with the construction of a transport database for the pediatric population, for reporting of adverse events and improvement of practices.
- With respect to response time for a specialized transport team, especially in a country like Sweden with significant geographical distances, a valuable study would be to investigate whether telemedicine could be a helpful tool for referring hospitals in the assessment before retrieval and for advice while waiting for the transport team to arrive.
- As stated by the SBU (see the Background chapter of the thesis) there are four steps in the evaluation of diagnostic tests with the last step being the question if outcome is better for patients undergoing the test compared with similar patients who did not undergo the test. Further studies are still needed to answer this question regarding NIRS utilization during inter-hospital transports. As a next step we plan to investigate the effect of altitude on oxygen extraction in transported children, to achieve this a pulse oximeter with capacity to download electronically stored continuous data would be necessary.

9 REFLECTIONS CONCERNING LEARNING OUTCOMES

This thesis project has taken more than five years to complete and it has been a continuous learning process from many sources.

The academic courses have been appropriate for this project and laid the groundwork to an increased knowledge on scientific thinking and general scientific methodology. By examining research articles and by theoretical studies during a course in methods for systematic literature review I have improved my skills in critical evaluation of research articles.

This knowledge has then been used in a very practical and obvious way in the process of working on a project from the formulation of a hypothesis and the methodological planning to analysis, interpretation and implementation of the results. Looking back, I can see how much I've learned from the process of working on Study I, which was strenuous and took a lot of time. In the same manner, the manuscript was difficult to write and took a long time to finish, moreover the initial submission was refused by two scientific journals before it was accepted by a third with major revisions. Indeed, this process was highly valuable, I had to be open to criticism and it made me reflect on my research in different contexts which I have benefited greatly from in terms of study limitations, interpretation of study results and how to improve its presentation in future scientific manuscripts.

The thesis has had a few different aspects i.e. epidemiologic studies as well as methodological studies with the application of a method, undoubtedly this has given me experience both in creating and conducting studies with different approaches and designs and the scientific breadth has been challenging but educative. By the work on this thesis I have gained experience in formulating a research hypothesis, creating a data base fit for use, in planning studies for a clinical setting and being prepared for unforeseen events which may occur and affect the implementation. The feedback from supervisors, co-authors and reviewers while revising manuscripts has been invaluable. I cannot overemphasize how much this has helped me in improving my ability to analyze and draw conclusions from my work.

Another great source of learning has been academic meetings where I've been given the opportunity to present my research either orally or as poster presentations. While preparing to present my research in such an environ-

ment I have had to reflect on weaknesses, how to summarize conclusions from my work, how to meet criticism and what results mean and how they contribute to the body of knowledge in this field.

Altogether, as a clinician since many years, it has been an absolute privilege to work with medicine from the research perspective. I have been even more fortunate since I have been able to conduct my research and this thesis in an area which I have been extremely interested in from a clinical perspective, and to combine it with research has been awesome. I have received invaluable help from my supervisors who have believed in me and this project and who have helped me to grow as a scientist. I am sure this academic training will be beneficial for my possibilities to contribute to future patient benefit, research and practice in health work.

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