ANTICANCER DRUG TREATMENT IN PEDIATRIC PATIENTS: STUDIES ON OPTIMIZING DOSAGE AND ON PARENTAL GUIDANCE FOR IMPROVED DRUG HANDLING AT HOME

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To Haifa and Jihad Akkawi

إلى أغلى الناس على قلبي....

"You have not been given of knowledge except a little"

(Surat Al-Israa, Verse 85)
ABSTRACT

Background: Every year about 370 children are diagnosed with cancer in Sweden. The treatment includes both inpatient and outpatient care with anticancer drugs. At the clinic, the optimal anticancer drug dosage is usually derived from the patient’s body surface area (BSA). However, several formulae for calculating BSA are available and knowledge about their accuracy and precision in children is scarce. Information on the best formula to use when the height of the patient is missing or cannot be measured is also lacking. Moreover, poor access to age-appropriate drug formulations can force parents to manipulate and handle oral anticancer drugs (OADs) at home without proper drug handling knowledge and skills.

Aims: The overall aim of the thesis was to increase knowledge on the adjustment of anticancer drug dosages for children in clinical practice and to optimize OAD handling procedures by parents in the home setting. The specific aims were: I. to validate Mosteller’s formula for calculating BSA; II. to test potential alternative formulae for estimating BSA using bodyweight (BW) alone; III. to observe the effects of risk-reducing strategies when handling high risk substances in the home setting; and IV. to describe parents’ experiences when handling OADs in the home setting.

Methods: Different methods were used in each of the four studies. Study I was an analytical retrospective study based on measured BSA values. Study II was a retrospective cohort study based on registered data from electronic health records. In Study III, we used an observational intervention study to observe parents while they handled OADs at home. In Study IV, we used qualitative methods with semi-structured interviews to obtain parents’ views.

Results: Study I showed that Mosteller’s formula underestimated BSA by 4.1 % in pediatric patients, and that inter-individual variability in the BSA measurements was most pronounced in neonates and infants. Study II showed that all three of the tested alternative formulae had good accuracy and precision for estimating BSA in children, using BW alone. Study III showed that many parents were handling OADs incorrectly at home before they were given an intervention. The intervention, which included practical training and information presented in different formats, improved the parents’ handling procedures significantly. Study IV resulted in four categories for the experiences of parents handling OADs at home: parents views on the provided information, with two subcategories: lack of, too little or contradictory information, and parents preferences for information delivery; safety over time; correct drug dosage; and drug administration.
Conclusions: In Study I we found that Mosteller’s formula should be used with caution in clinical practice because it underestimates the BSA of children, especially neonates and infants. Study II showed that any of the three tested alternative equations, using only BW, can be used as a substitute for Mosteller’s formula to calculate the BSA of children, including term neonates and infants, with the best fit from the Meeh-type equation. In Study III we found that an intervention comprising practical training and information presented in different formats should be provided to parents to enable them to handle OADs correctly at home. In Study IV we concluded that parents need to be provided with timely, clear, nonconflicting and repeated information presented in different formats and in their mother tongue.
LIST OF SCIENTIFIC PAPERS

This thesis is based on the following publications, which will be referred to in the text by their Roman numbers.

I. El Edelbi Akkawi R, Lindemalm S, Eksborg S.
   Estimation of body surface area at various childhood ages – validation
   of the Mosteller formula

II. El Edelbi Akkawi R, Lindemalm S, Nydert P, Eksborg S.
    Estimation of body surface area in neonates, infants, and children
    using body weight alone

III. El Edelbi Akkawi R, Eksborg S, Ekman J, Lindemalm S.
    Improved home management of oral pediatric anticancer drugs as a
    result of an intervention comprising practical training, written
    instructions and movie clips: a pilot study (Submitted)

IV. El Edelbi Akkawi R, Eksborg S, Kreicbergs U, Lövgren M,
    Wallén K, Ekman J, Lindemalm S
    Parent’s experiences when handling oral anticancer drugs at home: “It all
    falls back on me…” (Submitted)
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LIST OF ABBREVIATIONS

Acute lymphoblastic leukemia (ALL)

Body mass index (BMI)

Body surface area (BSA)

Bodyweight (BW)

Computerized physician order entry (CPOE)

Electronic health record (EHR)

Experience and evidence-based database for pediatric drugs in Sweden (ePed),

Healthcare professionals (HCPs)

Height (H)

Ideal bodyweight (IBW)

Interquartile range (IQR)

Karolinska hospital’s internal data warehouse (KARDA)

Lean bodyweight (LBW)

Maximum tolerated dose (MTD)

Mean prediction error as a percentage (MPE %)

Nordic Society of Paediatric Haematology and Oncology (NOPHO)

Oral anticancer drugs (OADs)

Personal protective equipment (PPE)

Root mean square prediction error (RMSE)

Total bodyweight (TBW)
1 INTRODUCTION

I was introduced to the complex world of pediatrics in 2010 when I began to work as a pharmacist in the pediatric drug group at the Astrid Lindgren Children’s Hospital. I quickly learned that children are not small adults and that safe and correct drug treatment for children needs the competence of nurses, physicians, and pharmacists. In 2012 I showed an interest in pediatric oncology, in particular in the work of professor Staffan Eksborg. My interest in pediatric oncology, drug dosage and drug handling grew with time. In 2014 I decided to start a pharmacist group within the NOPHO (Nordic Society of Paediatric Haematology and Oncology) to optimize drug treatment in children with cancer, with the help of pharmacists from the Nordic and Baltic countries. One of the included projects was to investigate the best method of reconstituting oral anticancer drugs (OADs) from tablets/capsules. I remember asking my colleagues in Sweden why oral suspensions from tablets/capsules are not reconstituted at the pharmacy, as is done in other Nordic countries. I was later provided with a letter dated to 2009 stating that the reconstitution of OADs at pharmacies was to be discontinued to protect pharmacy employees from the toxicity of the drugs. The focus of this thesis was conceived when I realized that we support healthcare professionals (HCPs) in handling and administering drugs correctly on the ward but we rely on parents to handle or manipulate the drug, and to give the correct dose to their child without sufficient support or guidance on safe, correct drug handling procedures in the home.
2 BACKGROUND

“If you take away a sick child from its parent or nurse, you break its heart immediately”
(Armstrong G, 1777)

It is known that the parent-child relationship is important not only to promote healthy growth and to strengthen bonding but also to support the child during different stages of stress in life, e.g. during hospitalization. At the end of the nineteenth century, parents were not allowed to visit their child in the hospital, to avoid the spread of infectious diseases [1, 2]. By the 1940s, pediatricians had discovered that children are likely to express psychological symptoms such as anxiety and depression when left without their parents during hospitalization [3]. However, it was not until 1970 that parents in Sweden could become a natural part of their child’s hospital stay. Today we know that parents play a central role during a child’s hospitalization and HCPs depend on parents from day one for help and support both on the ward and for home care [4-6]. Consequently, parents become responsible for their child’s drug treatment at home, and this can include handling high risk substances such as OADs that are intended to be managed by HCPs.

Every year about 370 children are diagnosed with childhood cancer in Sweden [7]. The treatment includes both inpatient and outpatient care, and optimal drug dosage is the core of successful treatment. In the clinic, body surface area (BSA) is the most common method of calculating the correct dosage of anticancer drugs. At home, the parents are responsible for preparing, managing and administering the correct dose to their child while adjusting to their new life situation as parents of children with cancer. This thesis contributes to the understanding of how parents experience anticancer drug handling and how drug dosage and drug handling could be optimized in clinical practice and at home.

2.1 CANCER IN CHILDREN

Cancer in children is rare, accounting for only 1 % of all cancers. Nonetheless, childhood cancer is one of the most common causes of death among children in Sweden [8, 9].

Childhood leukemias represent the largest group of childhood cancers and acute lymphoblastic leukemia (ALL) is the most common of these. The second most common form of cancer in children is tumors of the brain and spinal cord [7, 8].
2.1.1 Cancer treatment

“The difficulty of performing meaningful studies on the few patients treated in each pediatric oncology center has fostered the establishment of a large international cooperative group” Kotecha [12]

Before the first clinical trials were performed in the late 1940s, childhood cancer was regarded as fatal. Over the years, clinicians, nurses and pharmacists have organized themselves to optimize the care of children with cancer through close collaboration in both national and international groups [10-12]. These collaborative efforts have helped to optimize drug dosage, the use of multi-agent chemotherapy, and the care of children and their families, and have also helped to define the roles of radiation and surgery in the treatment of childhood cancer [10, 13].

2.1.1.1 Chemotherapy

“Survival rates for childhood cancers, many of which were fatal in the pre-chemotherapy era, have increased dramatically...” Saletta [14]

The overall survival rate for cancer in children has improved dramatically since the introduction of chemotherapy in the 1960s [14]. Most of the cancer forms that occur in children are sensitive to chemotherapy, in contrast to many cancers that occur in adults. This is due to the high cell proliferation rate in childhood cancer forms and the tendency for the cancer cells to undergo apoptosis [10].

The use of protocol-based therapy, including multi-agent chemotherapy administered at the highest tolerated dose, has contributed to an improved standard of care and outcomes in children with cancer [14, 15]. Progress in pediatric oncology care is not limited to improved survival rates but can also be seen in reductions in both short term and long term complications in children. The use of multi-agent chemotherapy in different drug forms helps to reduce the toxic side effects of any one drug, overcome drug resistance, improve survival rates, and allow prolonged drug exposure [10, 16]. Today, the most common treatment form in pediatric oncology is through an intravenous line. However, long term treatment with OADs is common in many pediatric oncology treatment protocols because it is cost-effective and convenient for the children and their parents [16, 17].
2.2 DRUG DOSAGE IN PEDIATRIC ONCOLOGY PATIENTS

2.2.1 The history of body surface area measurement

“These methods should not be accepted as a precise measurement of BSA, but rather as techniques which will allow comparison between individuals” Pinkel [43]

The first body surface area (BSA) measurements are believed to have been done by Leeuwenhoek (1719) in his study of the number of pores in the skin. Leeuwenhoek assumed that the BSA of an average sized man would be about 14 square feet, and he estimated the presence of 2,016,000,000 pores [18]. In 1879, Meeh constructed the first available formula for estimating BSA using only bodyweight (BW) [19]. Meeh’s formula was based on direct measurements of children and adults using the method of coating. The BSA was quantified by covering the whole or part of the body with a substance with a known or measurable area. In 1935, Edith Boyd obtained direct measurements of the BSA using a method involving coating, surface integration and triangulation, Figure 1 [18, 20]. She included subjects ranging from newborn children to adults. These measurements were later used to construct a formula for calculating BSA based on BW alone.

The DuBois brothers were the first to construct a BSA formula that included height (H) as an additional variable to BW [21]. However, their equation was based on measurements from only nine subjects, including only one child, resulting in unreliable nomograms [22]. In clinical practice the formula of DuBois and DuBois has now been replaced by Mosteller’s formula because it is easier to use and because of the unreliable DuBois nomograms. In Mosteller’s formula, BSA is estimated as the square root of H (in cm) multiplied by BW (in kg) divided by 3600 [23].

More than 25 formulae or nomograms have been described in the literature for calculating BSA, e.g. Sendroy and Cechini (1952); Haycock and Schwarz (1978); George and Gehan (1979); and Mosteller (1987) [24, 25]. Recently, BSA has been measured using a three-dimensional scan (3D), which has shown good reliability and repeatability [20]. A coating method using alginate also appears to have provided accurate assessments of BSA in Chinese adults, including obese subjects [26]. Some have queried the use of BW and H alone for calculating BSA, suggesting the inclusion of the head circumference as well [27]. Other researchers have proposed a BSA formula that takes sex, race and body shape into account [28, 29].
Computerized physician order entry (CPOE) methods (the use of computers instead of paper, phone or fax) are now widely used in clinical practice. HCPs use computers to enter medical instructions electronically, and are able to use complex formulae for calculating BSA easily and accurately during the drug prescription process.

**Figure 1**: Pictures taken from Boyd, 1935 [18].
A: The method of triangulation
B: The method of surface integration
C: The body was divided into 34 regions by Meeh to measure body surface area.

### 2.2.2 Dosage adjustment according to body surface area

“It should be recognized that children are not small adults, because the differences among neonates, infants, children, adolescents and adults are not merely due to body weight” Mahmood [33]

The growth of children is not a linear process, especially during the first years of life; the most extreme development rate is seen in neonates [30]. The maturation of different physiological factors and age-related changes in body composition can affect systemic drug exposure [31-33]. In neonates, infants, and children, both inter- and intra-patient variations in drug exposure need to be considered when assessing drug dosage, not only to achieve the desired clinical response but also to avoid toxicity [24]. This is especially important when deciding the dosage of anticancer drugs, which generally have a narrow therapeutic index (the range from the lowest effective dose to the maximum tolerated dose). Many physiological processes (e.g. drug metabolism, cardiac output [34], oxygen consumption [35], basal metabolic rate [36-38], blood volume [39, 40] and organ size [41]) are believed to be more closely correlated with BSA than with, for example, BW [41, 42]. BSA tables or
formulae are used to normalize the drug dose with respect to variations in age, body composition and body size [24, 36, 43].

In oncology practice, BSA has routinely been used to calculate the maximum tolerated dose (MTD) in an attempt to achieve the highest response rate [44]. Because BSA has a correlation with MTD, dosage adjustment according to BSA became the standard in pediatric oncology practice. However, BSA-based dosage has been criticized for its loose correlation with physiological parameters that are important for drug metabolism, such as clearance and glomerular filtration rate [45, 46]. Many of the BSA formulae currently in use have also not been validated for their use in the pediatric population. Nonetheless, BSA-based dosage adjustment is currently used in most pediatric oncology centers, possibly because of its long history (more than 50 years) of clinical experience [24, 47, 48].

2.2.3 Challenging situations for drug administration

2.2.3.1 Dosage adjustment in neonates and infants

“Unique and rapidly changing physiological characteristics contribute to unpredictable dose-exposure responses in this population” Ku [51]

The dosage of anticancer drugs is often based on BSA, but there are some exceptions. When prescribing drugs to infants weighing less than 10 kg, there are differences in addition to body size that must be acknowledged: greater surface to mass ratio, immature enzyme system, lower renal clearance, higher proportion of body water and lower proportion of body fat [49-51]. All these factors must be recalled when administering drugs to infants, especially drugs with a narrow therapeutic index such as anticancer drugs. Therefore, doses of anticancer drugs for infants weighing <10 kg are prescribed in terms of mg/kg instead of adjusting for BSA, to avoid toxicity. This cut-off is also recommended because the relationship between BW and BSA is assumed to be linear in infants, but not in older children [24]. However, for children weighing <10 kg, this strategy will result in a significant reduction in dose compared to older children whose dosage has been adjusted according to BSA.

In clinical practice, the dosage of a few drugs (e.g. antivirals and hydrocortisone) is currently adjusted according to BSA in neonates and infants. Even though the length (H) of newborns is hard to measure accurately, Mosteller’s formula or others containing H are still used to estimate the infants’ BSA [24, 52-54].
2.2.3.2 Dosage adjustment in obese children

“For the majority of drugs, the choice of dose will rely on empirical experience and application of the precautionary principle” Mulla [58]

Obesity changes both the composition and the physiology of the body, increasing circulating blood volume, cardiac output and renal blood flow [55, 56]. These changes can alter the pharmacokinetic parameters of a drug, mainly the volume of distribution, absorption and clearance, putting obese children at higher risk of toxicity or reduced therapeutic efficacy [57].

Currently, there are no clear recommendations on which BSA formula to use in obese patients. Most BSA equations seem to underestimate BSA in obese children which could result in underdosing of anticancer drugs. Verbraecken et al. recommended the use of Mosteller’s formula to predict BSA values for adult patients, including those who are obese [47]. Several other methods have been adopted in clinical practice for calculating the appropriate anticancer drug doses for obese patients. One common method is to cap the adjusted dose for a patient at a BSA = 2 m\(^2\) to avoid toxicity. Other strategies proposed as alternative measures to BW in obese patients include: total bodyweight (TBW), lean bodyweight (LBW) and ideal bodyweight (IBW) [33, 58, 59]. There is, however, no clear consensus on how to define IBW in children. There are at least three methods for calculating IBW and the dose can vary considerably depending on the method chosen [60]. Most of these dosage adjustment strategies have not been tested in clinical trials and could result in significant undertreatment and less favorable survival outcomes [61].

Obesity is a common complication of treatment among pediatric patients treated for childhood cancers [62]. There are currently no general guidelines for adjusting treatment for obese children and little guidance exists from the drug companies. In order to optimize drug dosage, the relationship between drug exposure and response must be understood. Therapeutic drug monitoring has been suggested as a method of individualizing drug dosage for anticancer drugs to avoid both the risk of underdosing, which could affect treatment efficacy, and high drug exposure, resulting in drug toxicity. In addition, because obese pediatric patients are rarely included in clinical trials, information concerning the impact of obesity on the pharmacokinetics and pharmacodynamics of certain drugs is not readily available [58, 63-66].
2.2.4 Other important factors during drug administration

2.2.4.1 Drug manipulation and dose accuracy

“The impact of manipulations on the efficacy of the drugs, the accuracy of the dose and any adverse effects on patients is not known” Richey [70]

Prescribing drugs that have not been labeled for use in the pediatric population is defined as “off-label” or unlicensed [67]. Many dosage forms are inappropriate for children and were provided by drug companies to suit the adult population. Poor access to age-appropriate pediatric formulations forces parents and HCPs to manipulate the drug in various ways to achieve the correct dose or to facilitate administration for a child [68]. Manipulation may be carried out by HCPs in the hospital setting just before administration, in the pharmacy during the preparation of extemporaneous medicines, or by parents in the home setting. The manipulation process can include dividing, crushing or dissolving tablets, or opening capsules and dissolving or suspending the contents [69]. In this thesis, the term manipulation refers to dividing (cutting) or dissolving tablets or opening capsules.

There are risks associated with these forms of drug manipulation. For example, manipulating drugs by splitting or crushing tablets can lead to changes in the drug pharmacokinetics profile and bioavailability, resulting in underdosing or risk of adverse effects [70]. Dividing or splitting a tablet, whether it has been scored or not, by hand, using a tablet splitter or using a kitchen knife, can result in an inaccurate dose [71, 72]. Dissolving or suspending tablets in water and then dividing the mixture or suspension can also result in inaccurate doses, especially if the drug is non-soluble in water. Drug loss during the manipulation step is also a significant problem which is highly dependent on the drug formulation, the person handling the drug, and the manipulation method used [70, 73].

The manipulated formulations are often administered to children by parents or carers without knowledge of the drug’s bioavailability, efficacy, or toxicity [74]. A study by Binson et al. revealed that manipulations of solid oral forms can lead to underdosing and unsafe situations such as skin contact with the drug powder. This was, however, not the case when the drug was prepared from commercially available oral suspensions [75]. Furthermore, crushing or breaking tablets into smaller parts can result in a bitter taste, which can influence the child's compliance towards a drug treatment.

Administration devices can be as important as the formulation itself in pediatric drug treatment. Liquid preparations are often dispensed from droppers, cup measures and
spoons. For increased accuracy during drug administration, especially for anticancer drugs, it is recommended that oral syringes are used for doses less than 5 mL [76].

There is a clinical need for more pediatric-friendly formulations for children, to facilitate the administration process and to increase dose accuracy.

2.2.4.2 Other factors to take into account
“The absence of an available pediatric dosage form for some medications increases the potential for dosing errors and may produce serious--sometimes fatal--complications in young patients” Skaer [85]

In addition to growth and developmental aspects, factors such as age, genetics, coexisting illnesses, previous chemotherapy/radiotherapy treatment, concomitant drug therapy, dosage forms, route of administration and adherence influence how children respond to a drug treatment [77]. Inborn or developed disease can lead to variability in drug response. For example, the usual dosage regimen for many drugs needs to be modified in patients with renal impairment to minimize the risk of toxicity [31, 78, 79]. Knowledge about the metabolic pathways of the drugs included in the treatment is important so that possible drug interactions can be identified. In the liver, the CYP450 enzyme system induces or inhibits the effects of some anticancer drugs, which can result in ineffective drug therapy or toxicity [10]. Genetic variations are common in the metabolic pathway in pediatric oncology. Genetic polymorphisms of some enzymes can dictate dose adjustments, for example a mutation in the thiopurine methyltransferase enzyme means it could be necessary to adjust the dosage of mercaptopurine to minimize the risk of bone marrow suppression [80].

Non-adherence to medication regimens and medication errors with pediatric oncology drugs are often linked to administration of OADs in the home setting. Studies in children with ALL have confirmed that non-adherence to OAD treatment regimens is associated with variability in drug response and increased risk of relapse. Medication errors in the home setting related to suboptimal medication use is common; for example, the wrong amount of oral suspension may be measured or the drug dose may not be adjusted according to the instructions of the HCP [81-84].

2.2.5 Other uses for body surface area
“The measurement of burn surface area is important during the initial management of burn patients for estimating fluid requirements and determining hospital admission criteria.” Livingstone [89]

The BSA is used in clinical practice not only to calculate optimal anticancer dosages but frequently also to make an accurate assessment of specific organ functions, e.g. cardiac
index, oxygen consumption and blood volume [47, 61, 85, 86]. In patients with chronic heart failure, the BSA is used as a prognostic indicator for adverse outcomes such as mortality [87]. In the operating theatre, BSA is a critical indicator of blood flow during cardiopulmonary bypass and cardioplegia. For patients with burn injuries, estimation of the BSA in combination with segmentation of the body to estimate the affected area (the rule of nines) is important for initiating therapy such as fluid intake and determining hospital admission criteria [88, 89]. The BSA is also used as an important variable for calculating treatment costs, e.g. for selecting an optimal size of vial for single use or for expensive drugs [90]. This is, however, difficult to apply in pediatric care where the prescribed doses are often small and vials customized for children are lacking.

2.3 DIAGNOSED WITH CHILDHOOD CANCER

“In the event of cancer, the whole family system is at risk” Woźniak [96]

Having a child diagnosed with cancer is one of the most stressful and overwhelming experiences a family can face. As well as absorbing the news that their child has a life-threatening disease, parents must obtain and incorporate the necessary knowledge and skills while balancing other life responsibilities and coping with their own distress [91, 92]. The child’s acute treatment and frequent hospitalization, and the parent’s responsibility for taking an active part in their child’s care both in hospital and at home, are highly stressful. Studies indicate that parenting an ill child is far more demanding and time-consuming than parenting a healthy child [17, 93]. Parental distress can have a negative impact not only on their physical and psychological well being but also on the functionality of the whole family [94, 95]. The new life situation incorporating increased childcare can also lead to a long period of work disruption and financial loss [96-98].

The initial reactions of parents when they are told about their child’s diagnosis include helplessness, feelings of uncertainty, and feeling emotionally, physically, and mentally drained. The highest levels of anxiety are reported during the time of diagnosis [99]. As time passes, the distress of the parents seems to decline as they tend to adapt to their child’s illness [100]. However, studies have indicated that even if their child is cured of cancer, many parents live in constant distress as they contemplate the possible late effects of the disease, the possibility of relapse, the child’s well-being, fertility and social life, and school-related issues [101-103]. Even siblings become involved in the new life situation, with some expressing strong emotions, unmet needs and difficulties dealing with the ill child’s suffering [94, 103-105].
Although a cancer diagnosis contributes to a lot of distress in the family’s life, studies have also demonstrated positive outcomes reported by parents: personal growth, pride in surviving the experience, improved parenting skills, and strengthened relationships within the family [101, 106].

Children with cancer experience distress associated with the diagnosis such as worry and fear of the unknown. The survival rates among pediatric cancer patients have increased in recent decades, and currently 75% of all children with cancer are cured as a result of more intensive treatment and the development of new drugs [104, 106]. However, more intensive treatment also means more pain and side effects such as fatigue, nausea, sore mouth, and constipation associated with medical procedures.

2.4 INFORMATION DELIVERY IN CANCER CARE

“Becoming a parent of a child with cancer conveys new responsibilities and roles, one of which is to understand about the disease and to know what to expect” Gibson [110]

Experiencing a cancer diagnosis is an emotionally overwhelming time for the whole family. At diagnosis, parents of children with cancer can have difficulty in absorbing and processing the information communicated to them [91, 105]. As the treatment proceeds, the distress seems to decrease and the parents’ ability to hear and understand the provided information is improved [100, 104, 107, 108].

The improved survival rate in childhood cancer and the shift in treatment to include more outpatient and at-home care have changed the context of communication about childhood cancer to parents [109]. Parents must be provided with accurate, timely, nonconflicting, repeated information at different time points to facilitate the care of their child, provide them with some sense of relief, and support the family to cope [110-113]. Studies have shown that most parents want to be informed about their child’s prognosis even if the information concerning the child’s diagnosis and treatment is upsetting [114, 115]. It is, however, known that both the process of communication and the transfer of information are complex [116]. When parents lack official information, they use alternative sources to seek information such as browsing the internet or questioning other parents in order to gain a sense of control [114, 117, 118].

Because different parents have different abilities to take in and internalize any given information, especially when their child’s illness has just been diagnosed, there is a need to educate HCPs about delivering consistent information to parents. Educational efforts, including practical training to enhance knowledge about complicated topics, are important.
The teach-back method is a comprehensive, evidence-based method which can help HCPs to verify that parents and patients have correctly understood the information provided, e.g. by parents demonstrating what they have learned prior to the child’s discharge [111, 122].

It is known that both the language ability and the culture of parents can be barriers to understanding the provided information; parents from different ethnic backgrounds are often under-informed by HCPs. There is a need to provide parents from different ethnic backgrounds with information in their mother tongue in order for them to fully understand it [123, 124]. The use of a standard method of informing parents that is individualized to their own needs and presented in different formats (written, movie clips and orally) and languages is important for delivering consistent, high-quality information [111, 125, 126].

The importance of answering the children’s questions about their disease and including them as active members in their own care is also becoming more and more acknowledged [117]. Children who receive information about their disease at diagnosis are less anxious and depressed than children who receive the information later in the treatment process [127, 128]. In addition, children aged between 4 and 10 years rely on parents to provide them with information. There is a need to educate parents in how to communicate with their children to optimize the delivery of information to the child [109].

2.5 HANDLING ORAL ANTICANCER DRUGS IN THE HOME SETTING

“Because oral anticancer drugs are self-administered, the responsibility of the “five rights” (i.e., right medication, right dose, right time, right route, and right patient) shifts from nurses to patients and caregivers” Rudnitzki [132]

Long term treatment with OADs is common in many pediatric treatment protocols; these protocols enable the parents to take over responsibility for the treatment from the HCPs and to prepare and administer the drug at home on their own [129-131]. Because there is a lack of age-appropriate formulations for children and because the compounding of child-friendly formulae in pharmacies was discontinued in Sweden to protect pharmacy employees from the risk of exposure, parents of children with cancer living in Sweden must manipulate the solid drug forms (i.e. tablets and capsules) themselves in order to give the correct dose or facilitate swallowing for their child. Parents are often unaware of the risk of handling OADs and patient bodily excretions [131, 132]. The handling process can be complex, which can increase the risk of incorrect and unsafe drug handling at home [82, 133-135].
International guidelines discourage the manipulation of solid anticancer drugs to protect both HCPs and parents from the toxicity of the drug. Parents are at risk of accidental exposure, e.g. when opening capsules and inhaling the dust, through dermal contact, from contaminated surfaces or bodily excretions, and when reusing personal protective equipment (PPE) or dosage equipment such as oral syringes [136-138]. The risks include exposure to substances with possible carcinogenic or reproductive outcomes [132, 139, 140]. Because there are no safe levels of hazardous drug exposure and because parents are responsible for manipulating and administering the drugs in the home setting it is necessary to educate parents/patients on the handling processes through practical training, and to supply them with educational materials in different formats and languages so as to ascertain safe handling of the OADs [132, 133, 141, 142].

2.6 THE ROLE OF THE CLINICAL PHARMACIST IN PEDIATRIC ONCOLOGY CARE

“The impact of an oncology pharmacist extends beyond individual patient care”
Oliveira [148]

Drug treatment in pediatric oncology care is a complex area that needs the competence of a multidisciplinary team to optimize and personalize treatment for each child. The chemotherapy protocols are already complex in this population, and inter-individual variability in the disposition and excretion of drugs in children, the off-label use of drugs, and the absence of age-appropriate formulations complicate the treatment further. The presence of a clinical pharmacist on the ward can ensure the safe and correct use and administration of chemotherapy and other high alert medications. In addition, pharmacists can support the nursing and medical staff with any drug-related questions, provide advice on cost-effectiveness, and help reduce medication errors [143-149].

Parent/patient education is an essential support for engagement of the parents in their child’s care and involving the patients in their own care. Education not only enhances skills and increases knowledge but also helps parents/patients to detect errors, especially regarding oral medications. Pharmacists and nurses play an important role in educating parents/patients in the proper handling of OADs, the use of PPE and drug disposal. Clinical pharmacists can also provide parents with essential information regarding their child’s drug treatment and answer parents’/patients’ questions and concerns [150, 151].

Recently, the pharmacist working group in the NOPHO, in cooperation with ePed (experience and evidence-based database for pediatric drugs in Sweden), had a meeting to reach consensus on creating best practice for handling OADs at home. The strategies
suggested were based on international guidelines, studies, and best practice methodology for handling anticancer drugs [40, 130, 136, 152-158].
3 AIMS AND RESEARCH QUESTIONS

The overall aim of the thesis was to increase knowledge on the adjustment of anticancer drug dosages for children in clinical practice and to optimize OAD handling procedures by parents in the home setting.

The specific aims of the thesis were:

I. to validate Mosteller’s formula for calculating BSA in pediatric patients;
II. to test potential alternative formulae for estimating BSA using BW alone in children aged 0 – 18 years;
III. to observe the effects of risk-reducing strategies when handling high risk substances in the home setting; and
IV. to describe parents’ experiences when handling OADs in the home setting.

3.1 RESEARCH FRAMEWORK

The research framework is presented in Table 1.

Table 1. Overview of the research questions and the overall research framework

<table>
<thead>
<tr>
<th>Study object</th>
<th>Research questions</th>
<th>Article</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation of Mosteller’s formula</td>
<td>How accurate and precise is Mosteller’s formula for estimating BSA in all pediatric patients?</td>
<td>I.</td>
<td>BSA was measured in 268 children and infants. BSA values were also estimated using Mosteller’s formula.</td>
</tr>
<tr>
<td>BSA calculation using only BW</td>
<td>Can Mosteller’s formula be used to test potential alternative formulae for estimating BSA using only BW?</td>
<td>II.</td>
<td>Registered data containing BW, H, sex and birth date were extracted from the EHRs stored in KARDA.</td>
</tr>
<tr>
<td>Oral drug handling in the home setting</td>
<td>What are the risks associated with parents handling OADs in the home setting?</td>
<td>III.</td>
<td>Parents were observed in their home settings. An intervention pilot study was carried out.</td>
</tr>
<tr>
<td>Parental experiences associated with OAD treatment at home</td>
<td>How do parents experience handling OADs in the home setting? How does inappropriate information delivery affect the parents?</td>
<td>IV.</td>
<td>Semi-structured qualitative interviews with parents were carried out.</td>
</tr>
</tbody>
</table>
4 MATERIALS AND METHODS

The methods used in this thesis are summarized briefly below. Detailed information may be found in the individual papers.

4.1 STUDY I

Design: An analytical retrospective study. The study was initiated to validate Mosteller’s formula, which is currently used in clinical practice to calculate BSA.

Setting: The study data were extracted from an international report (USA) which measured BSA, BW and H [18].

Participants: 49 neonates aged 0 - 28 days, 155 infants aged >28 days and <24 months, 44 children aged 2 - <12 years, and 20 adolescents aged 12 - 18 years were included. There were 86 female participants and 97 male participants; information concerning sex was missing for 85 participants.

Variables: The covariates collected from the international report were BSA, BW, H, and age.

Data source and measurements: Previously published data comprising measured BSA, BW and H were used to validate Mosteller’s formula. The BSA was measured using surface integration (N = 160), coating (N = 92) and triangulation (N = 16). These measured BSA values were compared with values estimated from Mosteller’s formula. The body mass index (BMI) was also calculated from the reported values of H and BW.

Study size: The study included all the pediatric patients in Boyd’s study, no power calculation was needed.

Quantitative variables: The variables included the number of patients, BW, H, BSA, BMI, median age, sex, and age-group (neonates, infants, children, adolescents) as defined by the European Medicines Agency [159].

Statistical methods: The Spearman rank correlation was used to test for correlations between the estimated and measured BSA values. Bias was expressed as the mean prediction error as a percentage (MPE %). The precision was calculated as percentage root mean square prediction error (RMSE %) [160]. The measured and estimated BSA values were compared using Eksborg’s plot [161]. The variance ratio test was used to compare the variability of data in two populations.
4.2 STUDY II

**Design:** A retrospective cohort study. The study was initiated to test potential alternative formulae for estimating BSA using only BW in children.

**Setting:** Registration data of interest were extracted from electronic health records (EHRs) in Karolinska hospital’s internal database for pediatric drugs (KARDA) from January 1 to December 31, 2013.

**Participants:** Pediatric patients aged 0 - 1 years, including 10,327 hospital admissions (3522 patients; 1481 female and 2041 male), and patients aged >1 - 18 years, including 17,113 hospital admissions (17,113 patients; 7290 female and 9823 male patients) were included. Patients with missing information on sex, H, or BW, or with a BMI >70, were excluded from the study. Pediatric patients older than one year were only included at the first hospital admission.

**Variables:** Covariates collected from KARDA were BW, H, sex and birth date.

**Data source and measurements:** Registered data including BW, sex, H and date of birth were extracted from KARDA from January 1 to December 31, 2013. Data were extracted from the day the child was registered or up to seven days after registration. The data were imported into an excel sheet and BSA was calculated using Mosteller’s formula. The calculated BSA values were plotted versus BW. BSA was then estimated from BW alone using nonlinear regression and three alternative formulae: a third order polynomial formula: $\text{BSA} = B_0 + B_1*\text{BW} + B_2*\text{BW} + B_3*\text{BW}$, a Meeh-type formula: $\text{BSA} = A*\text{BW}^B$, and a Boyd self-adjusting–type formula: $\text{BSA} = A*\text{BW}^{(B\cdot C\cdot \text{logBW})}$.

**Study size:** All pediatric patients registered at Karolinska University Hospital in 2013 were included. The huge number of included patients and hospital admissions was judged adequate for answering our research question.

**Quantitative variables:** Number of patients, hospital admissions, BW, H, BMI, sex, BSA and birth date.

**Statistical methods:** Results from the nonlinear equation were evaluated using Eksborg’s plot [161] and as recommended by Sheiner and Beal [160].
4.3 STUDY III

**Design:** An observational intervention study. The study was initiated to investigate any changes in OAD handling procedures in the home setting after an intervention.

**Setting:** Part 1: home observations conducted between October and November, 2019. Part 2: six to seven months after the first observations were made, parents were recruited to participate in the intervention. A pediatric nurse trained the parents on how to handle the OADs at home via a communication tool for video calls, Skype. After the intervention, observations were conducted via Skype between May and July 2020.

**Participants:** Parents of patients in a pediatric oncology center in Sweden during the study period were included for both parts. We excluded parents who did not have to manipulate the drug, were not able to communicate in Swedish without an interpreter or could not be reached by public transportation.

**Variables:** Four checklists based on best practice standards for handling OADs at home were constructed. Data were collected for each handling procedure, including: measuring an oral suspension, cutting tablets, dissolving tablets, and opening capsules.

**Data source and measurements:** Parents were observed and videotaped during their handling of OADs in the home setting. During the intervention, parents were trained by a pediatric nurse on how to handle OADs at home and provided with information on drug handling in different forms, Figure 2.

The checklists were used to score the OAD handling procedures for each parent individually. Each parent received a score of either 0 (incorrect/mishandled) or 1 (correct) for each step of the procedure.

**Study size:** The study included all parents of children with cancer during the study period. We aimed to include all manipulation procedures; 18 parents were included in part 1 and 15 parents in part 2.

**Quantitative variables:** The handling procedures were scored. The maximum possible scores (100 %) were 19 for handling an oral suspension, 18 for cutting tablets, 21 for dissolving tablets and 24 for opening capsules.

**Statistical methods:** Mann-Whitney U-tests were used to compare the two independent populations (part 1 and part 2 of the study). P-values < 0.05 were considered statistically significant.
4.4 STUDY IV

Qualitative approach: A qualitative approach was used to improve parents’ knowledge and understand parents’ experiences of handling OADs in the home setting. The specific aim was to describe the experiences of parents handling OADs in the home setting.

Qualitative data were obtained from semi-structured interviews in a pediatric oncology ward. A PhD student conducted interviews with each of the parents using a semi-structured interview guide. All interviews were audio recorded and transcribed verbatim.

An interview guide was developed and validated in two steps. The guide was first sent to experts in the field of drug handling to evaluate its content. After revision of the questions, eight pilot interviews of parents were carried out. No major revisions to the guide were subsequently required.

Sampling strategy: parents were selected using purposive sampling that took into consideration the form of the OAD, the manipulation method and the duration of treatment. Parents were excluded if they were not able to communicate in Swedish and did not have an interpreter. Eighteen parents were included. This number was considered sufficiently large and to include enough information-rich cases to address the specific aim.
Analyzing qualitative data: The data were analyzed using inductive qualitative content analysis. The data analysis started with a naive reading of each interview by all the researchers to capture the overall meaning. With the aim in mind, the interviews were then read through again following an organized format.

1) Meaning units were underlined, condensed and described by a code.

2) The codes were sorted into larger sets that eventually formed the categories and subcategories.

3) The categories and subcategories were discussed in the research group until consensus was reached.

MAXQDA-plus software (VERBI Software Consult Sozialforschung GmbH Invalidenstraße, Berlin, Germany) was used to apply codes to the transcript.

Validating qualitative data: the qualitative content analysis was validated through established concepts including: credibility, transferability, dependability and confirmability [162].

Trustworthiness

These validating concepts have been previously used in qualitative research to assess trustworthiness [162, 163]. The concept of credibility includes ensuring that the participants in the study are described well and that the sampling method and size are appropriate. Credibility helps to ensure the internal validity of the findings. Dependability describes the stability of the data (= data reliability) over time and under different conditions. Confirmability of findings means that the data are accurate and really represent what the participants said and not the researcher’s bias, motivation, or interest. Transferability describes whether the results can be extrapolated to other settings or groups.

4.5 ETHICAL CONSIDERATIONS

This thesis was conducted according to the Helsinki Declaration, World Medical Association, ethical principles for medical research involving human subjects, 1964 [164]. Studies II, III and IV had separate ethical permits from the Regional Ethical Review Board in Stockholm. Study I did not need an ethical permit because it included previously published data [18]. Study II included patient data without any personal identification numbers. In studies III and IV, participation was voluntary with the possibility of withdrawing from the study at any time. Informed consent was obtained and all participants were guaranteed full confidentiality.
5 RESULTS

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

5.1 STUDY I

In study I we compared published data of measured BSA values in children, with BSA values estimated by Mosteller’s formula. We found that the inter-individual variability in the measured BSA values in children aged 0 - 18 years was more pronounced in neonates and infants than in children and adolescents.

Evaluation of the predictive performance according to Sheiner and Beal [156] showed that Mosteller’s formula underestimated BSA in pediatric patients despite a very close correlation between measured and estimated BSA values ($r_s = 0.973; p < 0.00001$; Table 2).

Eksborg’s plot [157] demonstrated that 71.3 % (95 % CI: 65.4 – 76.6 %) of the quotients for estimated/measured BSA for the total pediatric population were within the accepted range of 0.9 – 1.1. However, Figure 3 shows that the precision of the estimated BSA values using Mosteller’s formula decreased with decreasing BW and H. The fraction of quotients for estimated/measured BSA within the range of 0.9 – 1.1 was significantly lower in neonates and infants than in children and adolescents ($p < 0.0259$; Figure 4, Table 2).

Figure 3. Measured and estimated body surface area (BSA) using Eksborg’s plot. A: a plot of the ratios of measured to estimated BSA versus bodyweight. B: a plot of the ratios of measured to estimated BSA versus height. BSA was estimated using Mosteller’s formula.
Figure 4. Measured and estimated body surface area (BSA) ratio in the various age groups. BSA was estimated from Mosteller’s formula.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>All participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8 months (0 - 18 years)</td>
</tr>
<tr>
<td>BSA</td>
<td>0.314 m² (0.122 - 2.13 m²)</td>
</tr>
<tr>
<td>BW</td>
<td>5.30 kg (1.28 - 98 kg)</td>
</tr>
<tr>
<td>H</td>
<td>63 cm (41 to 178 cm)</td>
</tr>
<tr>
<td>BMI</td>
<td>13.8 kg/m² (6.61 to 36.9 kg/m²)</td>
</tr>
</tbody>
</table>

Patient outcomes

MPE - 4.06 % (-5.071 to -3.041)
RMSE 9.38 % (8.39 - 10.28 %)

Coefficients of variation

- Neonates 9.81 (%)
- Infants 9.54 (%)
- Children 5.27 (%)
- Adolescents 6.60 (%)

Eksborg’s plots

- Neonates and infants 67.6 % (60.7 - 74.4 %)
- Children and adolescents 82.8 % (71.3 - 91.1 %)

Table 2. Data are expressed as median values and ranges (patient characteristics) and percentages and 95% CI (patient outcomes and Eksborg’s plot).

BMI = body mass index; BSA = body surface area; BW = bodyweight; H = height; MPE = mean prediction error; RMSE = root mean square prediction error.
5.2 STUDY II

The best fit of three nonlinear regression equations (third-order polynomial, Meeh-type [19], and modified Boyd self-adjusting-type [18]) to a plot of the calculated BSA values (Mosteller’s formula) versus BW was investigated. Eksborg’s plot and evaluations of the predictive performance according to Sheiner and Beal demonstrated that all three tested equations reliably estimated BSA from BW alone. For neonates with BW below 2 kg, the Meeh- and Boyd-type equations gave satisfactory estimates of BSA from BW alone (Figure 5, Table 3). For patients with BW exceeding 120 kg, all equations seemed to overestimate BSA (Figure 5).

We also found that the Meeh type of equation was the most suitable for estimating BSA from BW in the entire pediatric population, including neonates and infants with a BW from 1.4 to 10 kg (Figure 6, Table 3).

![Figure 5](image_url)

**Figure 5.** Estimation of body surface area from bodyweight. Results of nonlinear regression analysis. Green line: results from the third order polynomial equation; blue line: results from the Meeh-type equation; red line: results from the Boyd self-adjusting-type equation. Filled symbols: body surface area values calculated from Mosteller’s formula using bodyweight and height.

Figure 5A. Weight span: 0 – 160 kg.
Figure 5B. Weight span 1.4 – 10 kg.
Figure 6: Ratio of Meeh to Mosteller’s formula body surface area (BSA) values. Figure 6A. Data from neonates (aged 0 to 28 days); Figure 6B: data from infants (aged > 28 days to 2 years); Figure 6C: data from children (aged > 2 to 12 years); and Figure 6D: data from adolescents (aged > 12 to 18 years).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Polynom/Mosteller</th>
<th>Meeh type/Mosteller</th>
<th>Boyd type/Mosteller</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 28 days (n=2,648)</td>
<td>90.90</td>
<td>99.47</td>
<td>81.00</td>
</tr>
<tr>
<td>Percentage within 0.90 - 1.10</td>
<td>9.10</td>
<td>0.19</td>
<td>0.11</td>
</tr>
<tr>
<td>Percentage above 1.10</td>
<td>0.00</td>
<td>0.34</td>
<td>18.88</td>
</tr>
<tr>
<td>Percentage below 0.90</td>
<td>0.12</td>
<td>0.12</td>
<td>1.45</td>
</tr>
<tr>
<td>&gt;28 days - 2 years (n=9,796)</td>
<td>98.57</td>
<td>99.47</td>
<td>98.03</td>
</tr>
<tr>
<td>Percentage within 0.90 - 1.10</td>
<td>1.31</td>
<td>0.45</td>
<td>0.52</td>
</tr>
<tr>
<td>Percentage above 1.10</td>
<td>0.12</td>
<td>0.12</td>
<td>1.45</td>
</tr>
<tr>
<td>Percentage below 0.90</td>
<td>0.05</td>
<td>0.18</td>
<td>0.14</td>
</tr>
<tr>
<td>&gt;2 - 12 years (n=10,808)</td>
<td>99.30</td>
<td>99.48</td>
<td>99.55</td>
</tr>
<tr>
<td>Percentage within 0.90 - 1.10</td>
<td>0.61</td>
<td>0.43</td>
<td>0.41</td>
</tr>
<tr>
<td>Percentage above 1.10</td>
<td>0.09</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Percentage below 0.90</td>
<td>0.05</td>
<td>0.14</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt;12 - 18 years (n=4,188)</td>
<td>99.64</td>
<td>97.66</td>
<td>99.21</td>
</tr>
<tr>
<td>Percentage within 0.90 - 1.10</td>
<td>0.31</td>
<td>2.20</td>
<td>0.69</td>
</tr>
<tr>
<td>Percentage above 1.10</td>
<td>0.05</td>
<td>0.14</td>
<td>0.10</td>
</tr>
<tr>
<td>Percentage below 0.90</td>
<td>0.05</td>
<td>0.14</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Table 3. Results from Eksborg’s plots for body surface area (BSA) ratios
5.3 STUDY III

Observations in the home setting were carried out both before and after an intervention. Parents of children with cancer were first observed before the intervention during manipulation of OADs at home. The risks associated with drug handling were identified and risk-reducing strategies were constructed. During the intervention, parents were given practical training and were provided with information in different formats. The intervention significantly improved the handling of OADs among the studied parents. The median score for correct handling was 19 % [interquartile range (IQR): 3.6 to 30 %] before the intervention and 89.5 % (IQR: 71.5 to 94.5 %) after the intervention (p < 0.0001; Figure 7).

General procedures:

Before the intervention

Hand washing

Seventeen percent of participants washed their hands with soap and water before the drug preparation and 28 % washed their hands after completing the drug preparation.

Use of gloves

Only 22 % used new gloves, while 6 % re-used gloves during drug preparation.

Disposal of equipment and cleaning working area

None of the parents disposed of the used equipment in a sealed bag in the regular garbage or cleaned the working area after finishing drug preparation.

Figure 7. Handling procedures for oral anticancer drugs before and after an intervention. The figure shows the change in the handling score (percentage of the maximum scores for each handling procedure) before and after the intervention.

Unfilled symbols: scores before the intervention.
Filled Symbols: scores after the intervention.
After intervention

*Hand wash*

Seventy-nine percent of participants washed their hands with soap and water before drug preparation and 71 % washed their hands after completing the drug preparation.

*Use of gloves*

Ninety-three percent used new gloves and 0 % reused gloves during drug preparation.

*Disposal of equipment and cleaning working area*

Ninety-three percent disposed of the used equipment in a sealed bag in the regular garbage but only 57 % cleaned the working area after finishing drug preparation.

Procedure-specific data are presented in Table 4.

<table>
<thead>
<tr>
<th>Handling procedures</th>
<th>Before intervention</th>
<th>After intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Handling score</td>
<td>Handling score</td>
</tr>
<tr>
<td><strong>Oral suspension</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used adapter to measure the prescribed dose</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>Used new oral syringes</td>
<td>33%</td>
<td>80%</td>
</tr>
<tr>
<td>Re-used oral syringes</td>
<td>67%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Dissolving tablets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used new oral syringes/medical cups</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td>Re-used oral syringes/medical cups</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>Used an oral syringe with a cork</td>
<td>33%</td>
<td>67%</td>
</tr>
<tr>
<td>Washed spoon and glass cup with detergent and water, let air dry</td>
<td>0%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Cutting tablets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used tablet cutter</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Cleaned tablet cutter with detergent and water, let air dry</td>
<td>17%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Opening capsules</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Used new oral syringes</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Used new medicine cups</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>Re-used oral syringes</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>Washed spoon and glass cup with detergent and water, let air dry</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 4. Observations of parents during preparation of oral anticancer drugs for pediatric patients in the home setting.
5.4 STUDY IV

Parents of children with cancer were recruited to participate in an interview to discuss their experience of handling OADs at home. Important results were found from the qualitative content analysis. In total, 4 categories and 2 subcategories were identified: Parents' views on the provided information - lack of, too little or contradictory information, parents’ preferences for information delivery; safety over time; correct drug dose; and drug administration.

The experiences of parents handling oral anticancer drugs at home

At the beginning of the period of illness, the parents were overwhelmed by the amount of information they had to take in, understand and remember. As time passed, most parents began to get used to the situation and became more involved in their child’s drug treatment. Parents also reported taking more responsibility for the treatment both in hospital and at home. The parent’s way of taking responsibility was clearly presented throughout the whole illness path.

Results from the qualitative content analysis are briefly summarized below, by category and subcategory.

Category 1

Parents’ views on the provided information

Lack of, too little or contradictory information

When parents lacked information, they browsed the internet, checked the summary of product characteristics or approached other parents in the same situation for advice. Parents lacked standardized information on how to handle OADs at home. When parents lacked information, they found their own ways to solve the problem, for example they used scissors to open capsules.

Parents sometimes felt worried and confused when they received contradictory information from HCPs regarding drug handling. Not being supplied with PPE or materials for manipulating the drug complicated the process of drug handling for most parents.

“It is a lot; high demands on the parents; they have to take an active part in this game and have to have listened and captured all the needed information” (Mother #57).

Parents’ preferences for information delivery

The parents needed repeated, easily accessible, easy-to-understand information presented in different formats and in their mother tongue. Many parents also requested having their questions answered and getting feedback from HCPs during the drug handling process.
“It is never a disadvantage to get additional information, a video to watch... It would further enhance the whole thing, especially in the beginning when it felt very unusual and I was a little nervous, I would feel a little calmer” (Mother #26).

**Category 2**

**Safety over time**

With time, parents felt safer and found it easier to take in and process any given information from the HCPs. Parents also had many questions about their child’s drug treatment for which they needed an answer. The process of drug handling had become a part of the family’s daily routine.

“We are very used to that now and we have learned over time what to do” (Mother #20).

**Category 3**

**Correct drug dose**

Most parents were aware of the importance of achieving the correct drug dose, especially during drug manipulation. Giving an accurate dose was directly linked to the survival of their child. Some parents reported that the process of drug handling became more complex if the dose was hard to measure accurately.

“Oral solution that my child keeps in his mouth and then it drops out.... that you do not know either the amount of waste or how much he gets from the dose. It is such small differences that make such a big difference” (Father #16).

**Category 4**

**Drug administration**

The process of drug administration was reported by some parents to be difficult and filled with anxiety and sadness, especially if the parents had to force their child to take the medicine. To succeed with drug administration, the parents reminded the child about the hard times during treatment. Receiving support from HCPs during the child's first drug intake was much appreciated by the parents.

“In the beginning we almost felt that we were abusing our child, that we had to force him. It was very hard” (Mother #17).
6 DISCUSSION

6.1 KEY FINDINGS

In study I we found that: 1) the inter-individual variability in measured BSA values was most pronounced in neonates and infants; 2) Mosteller’s formula underestimated BSA in the pediatric population and should be used with caution in clinical practice because of low precision and accuracy, especially in neonates and infants.

In study II we found that: 1) any of the three investigated equations can be substituted for Mosteller’s formula (BSA from BW + H) to estimate BSA from BW alone in pediatric patients aged 0 – 18 years with high precision and accuracy; 2) the Meeh-type equation was the most suitable for estimating BSA from BW alone in the entire pediatric population, including neonates and infants.

In study III we found that 1) parents are not handling OADs correctly and safely without intervention comprising practical training, written instructions, and movie clips; 2) there is a great need to standardize the presentation of information given by HCPs concerning handling OADs in the home setting; 3) parents need to be educated on how to handle bodily excretions from their child correctly and safely at home.

In study IV we found that: 1) parents needed practical training and information presented in different forms before creating their own routines for handling OADs at home; 2) it was extremely important to parents that drug doses were accurately measured and the correct dose given as this was linked to the survival of their child; 3) when parents lacked information about their child’s drug treatment, they found their own way to solve the problem.

6.1.1 STUDY I: Validation of Mosteller’s formula

Direct measurements of BSA in children aged 0 – 18 years showed that inter-individual variability was wider in neonates and infants than in children and adolescents (Table 2). In addition, evaluation of the accuracy and precision using Eksborg’s plot revealed that 71.3 % of the quotients for estimated/measured BSA were within the range of 0.9 – 1.1 in the whole pediatric population. However, the BSA estimates for neonates and infants deviated from the measured values by up to 35 % (Figure 4). One might suspect inaccurate measurements of BSA, but Boyd reported high precision for her data. No information was given on the precision of the BW and H measurements [18].
Monitoring the growth of children is a routine part of physical assessments performed at birth and throughout infancy. Inaccurate and non-reproducible H measurements are acknowledged by HCPs, especially in newborns who prefer to remain curled up. In addition, newborns are soft and elastic in their extremities and H measurements are strongly dependent on how much you stretch out the child before the measurement [165, 166]. Variability in length measurements can be reduced if the methods used to measure H are standardized, especially in children < 2 years of age. Methods including practical training for nurses and the use of a recumbent length board are believed to improve the reliability of length measurements in pediatric patients [52, 167].

Mosteller’s formula seems to give highly accurate estimates of BSA (high r_s values). However, analysis by Sheiner and Beal showed that BSA values were underestimated using this formula (MPE %: -4.06 %) with a precision, expressed as RMSE%, of 9.38%.

Mosteller’s formula for the estimation of BSA has previously been validated in children (aged 1 month – 14 years) [168]. However, no information was presented on the accuracy and precision of the measurements used to evaluate its validity.

The question of whether BW and H are sufficient for calculating BSA remains open. A suggestion to include head circumference as an additional variable only resulted in minor improvements to BSA estimates [27]. The relationships between BSA, H and BW are believed to vary by race and some have suggested a need for individualization of the BSA equation to suit the local population [26, 47, 49, 169, 170].

Mosteller’s formula for estimating BSA has been used in clinical practice for ascertaining the dosage of many drugs, mainly in chemotherapeutics. Because the ability to metabolize and eliminate drugs varies among individuals, especially in neonates and infants, several guidelines on pediatric drug dosage adjustment based on developmental pharmacology have been presented [31-33]. In addition, dosage adjustments based on allometric scaling have been proposed as an alternative method for pediatric patients [171].

6.1.2 STUDY II: Estimation of body surface area using bodyweight alone

The BSA is an important method of evaluating clinical parameters such as cardiac function and renal clearance, and of determining the correct drug dose [25]. Mosteller’s formula is used to calculate BSA from BW and H for the entire pediatric population at the Astrid Lindgren Children’s Hospital, including for neonates and infants. The main finding in our study was that all three tested alternative formulae can be used as a substitute for Mosteller’s formula for calculating BSA from BW alone, with high precision and accuracy in pediatric
patients. However, the Meeh-type formula was the most suitable for children aged 0 – 18 years, especially for neonates and infants (Figure 6).

Dosage adjustments based on BSA were introduced to oncology practice in order to find a safe first dose in phase 1 clinical trials. Despite its limitations, BSA-based dosage adjustment is currently used in many treatment protocols [45]. However, most pediatric oncology protocols apply a cut-off point at a BW of < 10 kg for using BSA-based dosage adjustments, assuming a linear relationship between BW and BSA for this weight group [10]. This action will result in a significant dose reduction and risk of underdosing in this weight group compared to larger children receiving dosages adjusted according to BSA. Our results appeared to contradict the assumption of a linear relationship between BSA and H in neonates and infants (Figure 5B). However, in order to provide a more scientific approach to dosage adjustment for neonates and infants there is a need for more pharmacology and pharmacokinetic studies.

Given the difficulties in measuring H in children and in emergency situations when the H of the patient cannot be measured, and the effects this might have on the accuracy and precision of BSA measurements, it would be advantageous to be able to estimate BSA from BW alone. We modified the Meeh-type formula and the Boyd-type self-adjusting formula to suit pediatric patients of different ethical/racial backgrounds living in Sweden [29, 85, 172, 173]. The Meeh-type formula gave the best estimates for BSA for neonates and children and the Boyd-type self-adjusting equation gave the best estimates for adolescents. It should be recognized that all three of the tested formulae can be used to estimate BSA and that any differences in the accuracy and precision of the BSA calculations are believed to be of minor clinical importance.

Dosage adjustments according to BSA in obese patients remains under discussion; several strategies have been proposed for optimizing drug dosages for this group, including capping the dosage for a patient at BSA = 2 m², and adjusting the dosage according to TBW, LBW or IBW [58]. Livingstone et al. have proposed using a formula that only includes BW in obese patients since BW increases in obese patients without a proportional increase in H [88]. There is a need to perform more studies not only in obese patients but also in cachectic patients to optimize drug dosage adjustment according to BSA, because every substance and every patient is unique and the impacts of BSA can vary [174].

Our findings indicate that the Meeh type of equation is the best to use in clinical practice, especially in neonates and infants. Ahn et al. found that Meban’s formula is best for neonates
while Nwoye et al. found that Mosteller’s formula was most accurate in Saudi Arabian neonates [49, 50]. There is a need to modify existing formulae to suit populations of different races/ethnicities in order to optimize the calculation of BSA.

6.1.3 STUDY III: Improved home management of oral anticancer drugs

There is a lack of age-appropriate drug formulations for children, an increased practice of caring for patients as outpatients, and absence of regulations in Sweden to control the handling of OADs in the home setting. Consequently, parents and/or patients are required to manipulate OADs at home to get the correct dose or to facilitate drug administration, without supervision, proper education or follow up [40, 141, 175]. The manipulation processes are complex, which increases the risk of improper drug handling, inaccurate drug doses, medication errors and exposure of the whole family to toxic chemicals [73, 153, 176].

The results of this pilot study indicate that an intervention that included practical training and information presented in different formats, including written instructions and movie clips, significantly improved the handling of OADs at home by parents. These results are similar to those in a study that found that pharmaceutical counselling significantly decreased the knowledge deficit among parents in the management of OADs from 24 % to 8 % [129]. However, that study did not include observations of the handling procedures and nor did it include any educational effort. In another study, Tokdemir et al. used a standardized educational tool to educate adults about their oral drug treatment and found that patients’ adherence to medication schedules and self-efficacy (confidence in their ability to self-medicate) increased [177].

Manipulation of capsules is a complicated procedure; parents are often required to open the capsule and give their child half or a quarter of the contents. Besides the difficulty in obtaining an accurate dose, parents can also be subjected to more toxic dust than when handling tablets. There is an urgent need to support these parents with proper education and PPE until there are better solutions for the problem.

The observed handling procedures among the parents before the intervention showed variability in using PPE. They did not, for example, use gloves, or they reused gloves and oral syringes, and they often disposed of the PPE unsafely. It is assumed that handling medicines improperly is a result of lack of knowledge and that patient/parent education is important. There is currently no standardized way of educating parents in proper handling techniques and no organized way of providing parents with PPE in Sweden. Parents who did not use any PPE or reused PPE were not supplied with PPE, were not instructed to use PPE, did not have enough PPE, or actively chose not to use any equipment. These results are
similar to those in a study where only 10% of the parents used gloves, only 1% did not reuse gloves and only 50% used a tablet cutter [134].

There is currently a lack of knowledge among HCPs on how OADs should be handled at home. HCPs require regular education on this topic in order to standardize and optimize delivery of information to parents/patients. Parents should be educated on handling procedures using different educational forms, especially for complex procedures [131, 178-180]. Parents with non-Swedish backgrounds need to be provided with materials in their mother tongue so as to be able to understand the handling procedures [181]. Clinical pharmacists should be included in patient education, not only to help parents with handling OADs at home but also to support and follow up on the drug treatment, the handling of bodily excretions and answering questions and concerns [182].

**6.1.4 STUDY IV: The experiences of parents handling oral anticancer drugs at home**

Although OADs are convenient and offer many advantages for both the patient and the family [183], problems have been identified when they are managed at home. Beside the burden of having a sick child, parents must carry the additional burden and responsibilities of handling and administering OADs at home, without being prepared [104, 111]. In this study, parents expressed a lack of knowledge regarding correct drug handling, correct handling of bodily excretions, avoiding drug exposure, obtaining the correct drug dose and administering the drug to their child.

Parents reported different levels of satisfaction regarding the information provided by HCPs about handling OADs at home. Some parents reported receiving sufficient information and others reported receiving insufficient information. Many parents were not aware that OADs should be handled with caution and this in addition to the lack of a standardized way of informing parents about handling OADs might have contributed to their lack of satisfaction. Some parents felt they had received contradictory information regarding handling OADs in the home setting [181, 184]. The receipt of contradictory information gave them a sense of insecurity and mistrust towards the HCPs. It has been reported that parents often receive mixed messages from different HCPs, which leads to frustration and confusion [100, 113, 119, 125].

The lack of standardized information and the lack of a good structure for informing parents about handling OADs at home both affected the timing of information delivery. Parents need to be informed about handling OADs in conjunction with the OAD treatment and before
creating a routine that works for the family. Information given at the right time helps parents to understand the given information and to do it right from the beginning [121, 185].

HCPs need to support parents in handling the challenges of managing OADs at home by providing them with information and answering questions and concerns. There is limited information about the best method of delivering information to parents. In this study, parents reported that being provided with information in different forms and in their mother tongue was preferable. There is also a need to follow up and remind parents about safe correct handling of OADs at home in addition to the initial education program on how to handle their child’s medication [186]. Studies have suggested that the inclusion of a pharmacist in patient education, including a regular follow up, could be helpful for the parents/patients [181, 187].

The withholding of information with the idea that it is in the patient’s/parent’s best interests, a form of paternalism, is still common in clinical practice [188]. In our study, only 17% of the parents reported being provided with information on how to handle bodily excretions at home. Some HCPs might have chosen not to inform patients/parents on how to handle bodily excretions to protect them from anxiety. However, in some cases HCPs themselves may be unaware of the risks associated with handling OADs and the bodily excretions of patients receiving them [130, 131]. There is a need to educate parents about correct handling of bodily excretions and to standardize the information provided by HCPs.

The parents in this study were clearly aware of two problem areas: obtaining the correct drug dose and challenges during drug administration. There is a need to support the child and the parents during drug intake through practical drug administration training and support. There is also a need to include the children in their own drug treatment so as to facilitate the drug administration process. Future studies should focus on the children, their requirements for drug administration, and their preferences for drug formulations.

6.2 METHODOLOGICAL CONSIDERATIONS
The following methods were used in this thesis: the use of published measured BSA data, extraction of data from EHRs, an intervention study where parents were video-filmed at home, and semi-structured interviews of parents. This variation in techniques contributes to the strength of the thesis. The strengths and limitations of the studies are described in detail below.
6.2.1 Quantitative research

In Study I we controlled for the risk of selection bias by including all the children described in Boyd’s study. There may be a risk for selection bias in Study II because we only included patients for whom both H and BW were recorded. Registration of BW is mandatory at our hospital, but this is not the case for other measurements; for example, the patient’s height might only have been registered when there was specific clinical interest (e.g. patients with a growth disorder). To minimize the risk of selection bias, we included a large number of patients in the study. Study III had only a small sample size, parents with newly diagnosed children were not included, and the study only included one pediatric oncology center. We did, however, include all manipulation procedures occurring both before and after the intervention.

It is unfortunately not possible to validate the measured BSA values in Study I; however, high precision was reported by Boyd. There was no information on the precision of the measured BW or H data, nor on the method used for measuring H. Another possible bias was the lack of information on the time of day that the H measurements were made (there is a natural variation in body length during the day). One strength of Study I was the use of several methods to validate Mosteller’s formula. Eksborg’s plot were used in addition to predictive performance methods.

No data were manually corrected in the excel file in Study II. There is a possibility that incorrectly registered parameters such as H and BW might have influenced the BSA calculations. However, the impact of this on our calculations was regarded as negligible because of the huge number of included patients. In Figure 6, the Eksborg’s plot for the Meeh-type/Mosteller BSA ratio as a function of age in the four age groups showed evenly distributed data above and below 0.9-1.1, indicating a lack of systematic errors.

The use of Mosteller’s formula as the gold standard against which to test our data could be considered another drawback. We showed in Study I that Mosteller’s formula underestimates BSA in children. However, Mosteller’s formula is incorporated in the CPOE methods at our hospital and its use is based on good clinical experience.

The Hawthorn effect should be acknowledged in Study III since many parents may have handled the OADs correctly after the intervention only because they were being observed [189]. All observations after the intervention were conducted via Skype because of the Covid-19 pandemic. We were not able to visit the parents in the correct context as done before the intervention and this can be seen as a limitation of the study. The strength of this
study was the combination of information given in different forms, including practical training using the teach-back method. A combination of different methods for learning gives the best outcomes according to a Cochrane review [190].
6.2.2 Qualitative research

In order to achieve and increase trustworthiness in Study IV, the design of the study, the manner of recruitment of participants, and all the steps during the data analysis process were clearly explained. Purposive sampling was used to include parents with varied diagnoses, ages, drug forms and lengths of treatment, which enriched the data variability and consequently strengthened the study credibility. The number of included patients was considered sufficiently large to ensure enough information-rich cases to describe parents’ views on the information provided [191]. The interview guide used during the interviews was validated and tested on parents before its use in the study, which strengthened its validity. The same guide was used through all the interviews both before and after the intervention, providing consistency and thus strengthening dependability [192]. To show confirmability, all the authors were involved in the analytical process as well as the development of the included categories and subcategories to minimize the risk of pre-assumptions and to strengthen the credibility of the study. Trustworthiness was further enhanced by selecting quotations from some parents.

Results from qualitative data analysis cannot be generalized but can be transferred to other settings and groups [193]. The results from this study could give new insight into drug handling by parents in the home setting for diagnoses other than childhood cancer. The results could help HCPs to individualize the delivery of drug information to parents.

6.3 CLINICAL IMPLICATIONS

The clinical implications of Studies I-IV are summarized below.

To facilitate and secure the handling of OADs at home there is a need to:

➢ Reintroduce the concept of pharmacy-reconstituted OADs in Sweden to decrease the risk of exposure for families.

➢ Implement practical training for parents and provide them with information presented in different formats and languages in all oncology centers in Sweden. The information should be distributed through ePed, a national evidence-based database for pediatric medicines that provides information for HCPs, patients, and parents.

➢ Supply parents with PPE that is easily accessible and can be delivered to the patients’ homes.
Have a clinical pharmacist or nurse on the ward who can answer parents’ questions and address their concerns. Contact with the pharmacist or nurse should be available in different forms, e.g. through direct contact, online chat, e-mail or phone.

Help the child and the parents with the process of drug administration through practical training on the ward before leaving for home, with the help of experienced nurses.

To standardize the presentation of information given to parents there is a need to:

➢ Educate HCPs on handling OADs and bodily excretions, preferably by clinical pharmacists who are experts in drug handling.

➢ Provide parents with information and practical training on handling OADs at home in conjunction with the prescription of OADs and before they create their own routine at home.

The use of BSA in clinical practice

➢ Mosteller’s formula is the gold standard used at our hospital and is associated with extensive clinical experience. However, the formula should be used with caution in children, especially in neonates and infants, because it underestimates BSA. When using Mosteller’s formula, the clinicians should evaluate whether this underestimation is of clinical importance considering both patient- and drug-related factors.

➢ There is a need to implement one of the three formulae investigated in this thesis (the third order polynomial equation, the Boyd self-adjusting equation and the Meeh-type equation) in the CPOE system in all hospitals in Sweden that have pediatric wards. The chosen formula should be easily accessible when there is a need to calculate BSA using only BW, e.g. in emergency situations. The Meeh formula should be prioritized, however, because it provides reliable estimations of BSA in all children, including neonates and infants.
7 CONCLUSIONS

- Mosteller’s formula underestimated BSA in children and should be used with caution in clinical practice, especially in neonates and infants where there is wide inter-individual variability.

- Any of the three tested alternative formulae can be substituted for Mosteller’s formula to calculate BSA in children when an accurate H of the patient is not available. For term neonates and infants, the Meeh formula fitted best for calculating BSA from BW alone.

- An intervention comprising practical training and information presented in different formats significantly improved the handling of OADs at home by parents. There is a need to standardize the delivery of information given by HCPs and to provide parents with PPE for handling OADs at home safely and correctly.

- Parents need to be provided with information on how to handle OADs at home that is clear, non-conflicting, given at the correct time, repeated, and presented in different formats and in the mother tongue of the recipient.

8 FUTURE PERSPECTIVES

- In this thesis we found that Mosteller’s formula underestimates BSA, especially in neonates and infants. In future studies it would be interesting to validate other BSA equations, especially those recommended for neonates and infants, e.g. Meban’s formula.

- In Study II, BSA was calculated using Mosteller’s formula. In future studies it would be interesting to substitute the calculated BSA values (obtained using Mosteller’s formula) with the BSA measurements in Boyd’s study, or with BSA values obtained from a three-dimensional scan, to estimate BSA from BW alone using non-linear regression.

- National multicenter studies on how parents handle OADs at home before and after an intervention comprising practical training and information presented in different formats also need to be performed. In these studies it would be interesting to include parents of newly diagnosed children, a variety of OAD drugs, more patients requiring capsules to be opened, and diagnoses other than ALL and brain tumors.

- It would be interesting to perform a study on parents of newly diagnosed children with cancer to evaluate learning outcomes about drug handling at home. The parents could be randomized into three groups: 1) a control group (receiving routinely
provided information), 2) parents receiving information in different formats and languages (intervention), and 3) parents receiving pharmaceutical counselling (intervention). The learning outcomes could be evaluated through a questionnaire.

➢ In Study IV, we noticed that parents had difficulties when administering the medicines to their children, especially at the beginning of the oral drug treatment program. It would be very interesting to conduct interviews with children receiving OADs to discuss how they feel about drug intake and what could facilitate and/or complicate the process of drug intake.

➢ In this thesis, the processes of handling drugs and bodily excretions were discussed only with parents. It would be interesting to form focus group interviews with nurses to discuss their views on handling OADs at home, including the handling of bodily excretions.

Idag saknas barnanpassade beredningsformer för många orala cytostatika i Sverige. Innan 2009 ansvarade apoteket för att ta fram läkemedel i flytande form från tabletter och kapslar. Apoteket valde därefter att lägga ner verksamheten av orala cellgifter för att skydda personalen från att exponeras för läkemedlets toxiska effekt. Idag bär föräldrarna ansvaret för att göra iordning samt administrera läkemedel till sitt barn utan tillräckligt med stöd för att en korrekt och säker hanteringen i hemmet.

Syfte: Avhandlingen syftar till:

- Utvärdera Mostellers formel för uträkning av kroppsyta hos barn.
- Testa tre potentiella formler för uträkning av kroppsyta där endast kroppsvikt är inkluderad.
- Öka förståelsen för hur föräldrar hanterar orala cytostatika i hemmet både före samt efter stöd för korrekt hantering i hemmet.
- Beskriva föräldrarnas erfarenheter av att hantera orala cytostatika i hemmet.

Metoder: Följande metoder har använts i avhandlingen:

- Värden från barn med känd kroppsyta, kroppsvikt och längd användes för beräkning av kroppsyta med hjälp av Mostellers formel.
• Kroppsvid och längd på barn mellan 0 – 18 år användes för beräkning av kroppsyta med hjälp av Mostellers formel. De uträknade värden låg till grund för att testa tre nya formler för uträkning av kroppsyta med hjälp av endast kroppsvid.

• Vi observerade hur föräldrar hanterar orala cytostatika i hemmet genom att videofilma hantering förloppet (till exempel vid tablettdelning) både innan föräldrarna fick stöd i form av praktisk träning och information samt efter stödet.

• Vi intervjuade föräldrar till barn med cancer, föräldrarna fick svara på olika frågor hur de upplever hanteringen av orala cytostatika i hemmet samt hur de ser på informationen de har mottagit av vårdpersonalen.

• **Resultat:** Resultat från de fyra inkluderade studier I avhandlingen:

  • Mostellers formel underskattade kroppsytan på barn med 4.08 %. Variabiliteten för den uppmätta kroppsytan var mest uttalande för nyfödda samt barn upp mot 2 år.

  • Alla tre formler som testades för att räkna ut kroppsytan på barn genom att endast inkludera kroppsvid visade god precision och riktighet.

  • Föräldrar hanterade orala cytostatika på ett inkorrekt sätt innan de fick stöd av vårdpersonal. Stöd I form av praktisk träning och information presenterad på olika sätt förbättrade föräldrarnas sätt att hantera orala cytostatika i hemmet.

  • Vi intervjuade föräldrar till barn med cancer och svaren sammanställdes I följande kategorier och subkategorier: Föräldrarnas syn på den erhållna informationen, **Avsaknad, otillräcklig eller motsägande information**, Föräldrarnas preferenser för hur information ska presenteras, Säkerhet över tid, Rätt läkemedelsdos, Läkemedelsintag.

• **Slutsatser:**

  • Kroppsytan beräknad med Mostellers formel bör användas med försiktighet I klinisk verksamhet, speciellt för nyfödda barn.

  • Det är möjligt att räkna ut kroppsytan hos barn genom att endast använda kroppsvid.

  • Föräldrar bör erhålla information från vårdpersonal presenterad på olika sätt inklusive praktisk träning för att hantera orala cytostatika på ett korrekt sätt i hemmet.

  • Föräldrar till barn med cancer ska förses med tydlig, ej motsägelsefull, upprepad information given vid rätt tidpunkt och på deras modersmål.
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