

**LIFE-CHANGING TREATMENTS IN CENTRAL NERVOUS
SYSTEM DISEASES: VENTRICULOPERITONEAL-SHUNT AND
TARGETED THERAPIES**

Ph.D. Thesis

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"Science is magic that works."

– Kurt Vonnegut

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1. LIST OF ABBREVIATIONS

AISC	Antibiotic-Impregnated Shunt Catheter
AUC	Area Under the Concentration–Time Curve
BSA	Body Surface Area
BMI	Body Mass Index
CI	Confidence Interval
CL/F	Apparent Clearance
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 Enzyme Family
DNA	Deoxyribonucleic Acid
FDA	United States Food and Drug Administration
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HRMS	High-Resolution Mass Spectrometry
I ²	Heterogeneity Index in Meta-Analysis
LC-MS/MS	Liquid Chromatography–Tandem Mass Spectrometry
MAPK	Mitogen-Activated Protein Kinase
MEK	Mitogen-Activated Protein Kinase Kinase (MAP2K)
MRI	Magnetic Resonance Imaging
NF1	Neurofibromatosis Type 1
OR	Odds Ratio
PBPK	Physiologically Based Pharmacokinetic Model
PD	Pharmacodynamics
PK	Pharmacokinetics
PN	Plexiform Neurofibroma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RNA	Ribonucleic Acid

SD	Stable Disease
SEM	Standard Error of the Mean
SPRINT	Selumetinib in Pediatric NF1 Trial (ClinicalTrials.gov NCT01362803)
TDM	Therapeutic Drug Monitoring
VP	Ventriculoperitoneal
WHO	World Health Organization

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My long-term vision is to improve outcomes in paediatric oncology through personalised, evidence-based strategies that address both treatment efficacy and the prevention of complications. I believe that integrating clinical practice with translational research is the most effective way to advance care for children with cancer and genetic tumour predisposition syndromes. My mission is to build a career that bridges clinical paediatric oncology and translational pharmacology, with a special focus on neurofibromatosis type-1 (NF1) and targeted therapies. I am dedicated to:



- Reducing preventable complications (e.g., shunt infections) through systematic evidence and clinical innovation.
- Implementing therapeutic drug monitoring (TDM) and pharmacogenetics to optimise individualised targeted therapy.
- Strengthening international collaborations to bring cutting-edge therapies and research opportunities to Hungarian and Central European paediatric patients.

2.2. Scientometrics

Number of all publications:	6
Cumulative IF:	12.9
Av IF/publication:	2.12
Ranking (SCImago):	D1:1, Q1:3, Q2:1
Number of publications related to the subject of the thesis:	2
Cumulative IF:	7.3
Av IF/publication:	3.65
Ranking (Sci Mago):	D1:1, Q1:1
Number of citations on Google Scholar:	10
Number of citations on MTMT (independent):	8
H-index:	2

The detailed bibliography of the student can be found on pages 46-47.

2.3. Future plans

Over the next five years, I aim to establish a multicentre collaboration focused on neurofibromatosis type 1 (NF1) and the pharmacokinetics of selumetinib, integrating genetic and metabolic profiling with therapeutic drug monitoring (TDM). In parallel, I aspire to contribute to the development of clinical guidelines on targeted therapies and the prevention of treatment-related complications in paediatric oncology, with the ultimate goal of improving personalised care and long-term outcomes for children with cancer.

3. SUMMARY OF THE THESIS

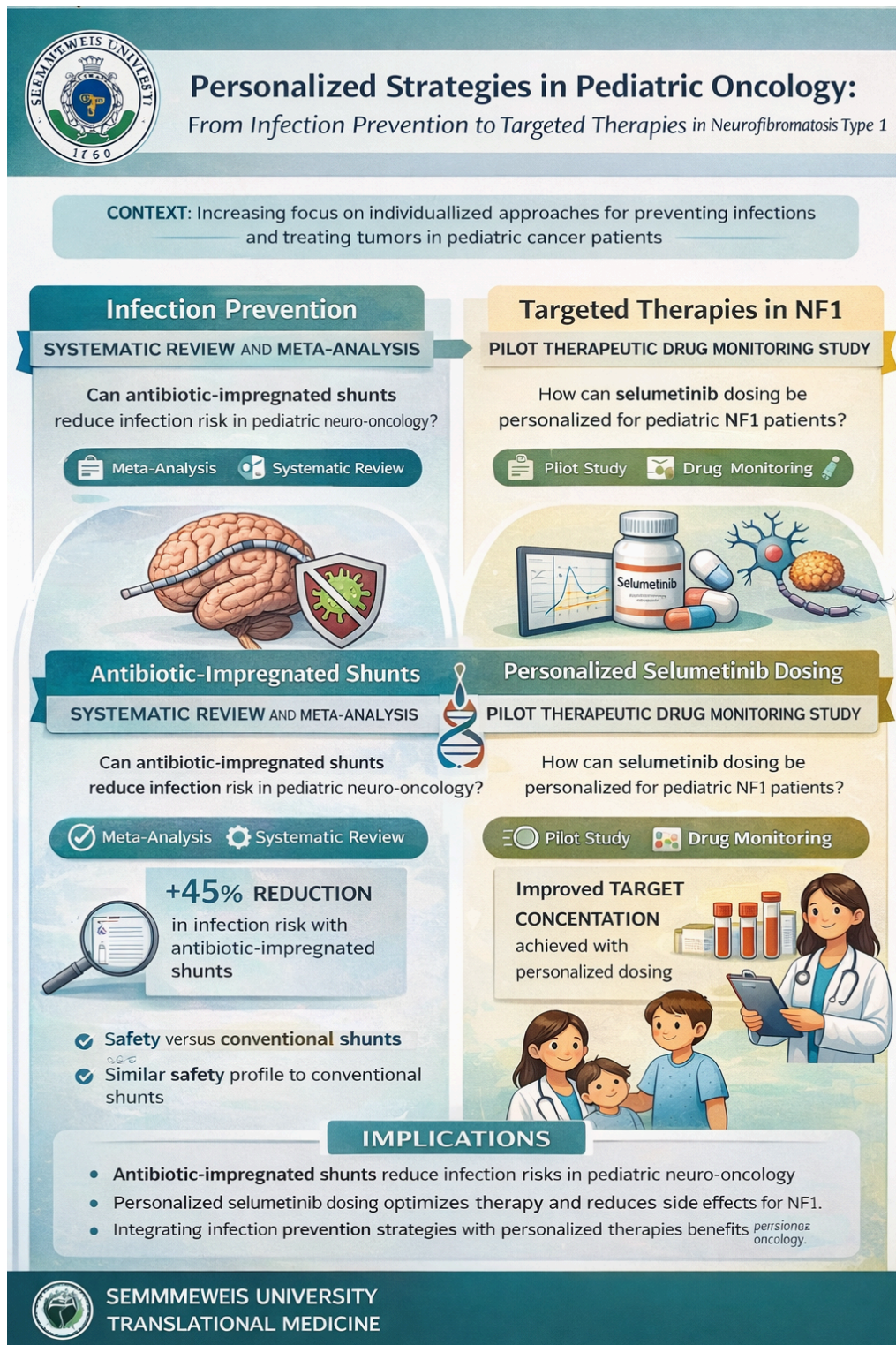
Paediatric oncology has transitioned toward precision-based care, aiming not only to improve survival but also to reduce treatment-related harm. This thesis explores two complementary approaches to precision medicine: prevention of infectious complications and individualisation of targeted therapy. Although conducted in different clinical settings, both studies focus on improving safety and effectiveness through evidence-based, patient-specific strategies.

The first study, a systematic review and meta-analysis published in *Neurosurgery* (2024), evaluated the effectiveness of antibiotic-impregnated ventriculoperitoneal shunt catheters. Data from 27 studies involving more than 27,000 procedures demonstrated a significant reduction in bacterial shunt infections compared with standard catheters (OR: 0.42; 95% CI 0.30–0.58). The protective effect was most evident in paediatric and infant populations. Evidence quality was moderate, and available cost analyses suggested potential healthcare savings. These findings support the routine use of antibiotic-impregnated shunts in paediatric neurosurgery.

The second study was a prospective pilot investigation of 22 paediatric patients with neurofibromatosis type 1 treated with the MEK inhibitor selumetinib. Despite standardized body-surface-area-based dosing, substantial interindividual variability in drug exposure was observed. Higher exposure levels were associated with increased toxicity, particularly dermatologic and muscular adverse effects. Therapeutic drug monitoring using LC-MS/MS proved feasible in clinical practice, and a preliminary therapeutic exposure range was proposed to support individualised dosing.

Together, these studies demonstrate how precision medicine in paediatric oncology extends beyond genomics to include infection prevention and pharmacokinetic optimisation. By integrating evidence-based prevention with individualised treatment, this thesis contributes to safer, more effective, and more patient-centred paediatric care.

4. GRAPHICAL ABSTRACT



5. INTRODUCTION

5.1. Overview of the topic

5.1.1. *What is the topic?*

Over the past half-century, paediatric oncology has evolved from an empirically driven discipline into one increasingly guided by molecular, pharmacological, and technological precision (1, 2). Whereas treatment was once dominated by broadly acting chemotherapeutic regimens, contemporary paediatric cancer care is characterised by targeted therapies, molecular diagnostics, and a growing emphasis on reducing treatment-related toxicity (1, 3). The guiding principle of this transformation is precision medicine, defined as delivering the right intervention to the right patient at the right time (4, 5).

This thesis addresses two complementary dimensions of precision medicine in paediatric oncology: prevention of avoidable complications and individualisation of therapy. Specifically, it investigates infection prevention in paediatric neurosurgical patients and pharmacokinetically guided dosing of targeted therapy in children with a genetic tumour predisposition syndrome. Although these topics arise from different clinical contexts, both aim to improve safety and effectiveness through evidence-based, patient-specific approaches.

5.1.2. *What is the problem to solve?*

Children with cancer and cancer-related conditions are uniquely vulnerable to both disease-related and treatment-related harm (1). Their developing organs, limited physiological reserves, and long-life expectancy magnify the consequences of complications such as infection, neurotoxicity, growth impairment, or chronic organ damage. In this context, two major unresolved challenges persist.

First, infection remains a leading cause of morbidity in paediatric oncology and neurosurgery (6, 7). Ventriculoperitoneal shunt infections in children with hydrocephalus represent a particularly severe yet potentially preventable complication, often resulting in repeated surgeries, prolonged hospitalisation, and long-term neurological sequelae (7, 8). Despite the availability of antibiotic-impregnated shunt

catheters (AISC), uncertainty has existed regarding their true effectiveness, especially in infants and young children (9-11).

Second, the increasing use of oral targeted therapies has revealed substantial interindividual variability in drug exposure and toxicity (12-14). Standard body-surface-area-based dosing does not adequately account for differences in absorption, metabolism, and clearance among paediatric patients (14, 15). In children with neurofibromatosis type 1 treated with selumetinib, this variability can lead to either suboptimal efficacy or clinically significant adverse effects, highlighting the need for more individualised dosing strategies (1, 16).

5.1.3. What is the importance of the topic?

Optimising safety while maintaining therapeutic efficacy is a central goal of modern paediatric oncology (1, 4). Preventing infections and minimising treatment-related toxicity are not secondary concerns but essential components of high-quality care, as complications can compromise survival, quality of life, and long-term outcomes.

Infection prevention strategies such as antibiotic-impregnated shunt catheters have the potential to eliminate predictable harm in high-risk populations, particularly infants and immunocompromised children (9, 11). Similarly, therapeutic drug monitoring represents a powerful tool for managing variability in targeted therapies, enabling clinicians to balance efficacy and toxicity based on measurable pharmacokinetic data (14, 15, 17).

Addressing these issues is especially important in paediatrics, where the consequences of inadequate prevention or improper dosing may affect patients for decades. Therefore, evidence-based approaches that improve safety and personalisation are highly relevant clinically, ethically, and economically.

5.1.4. What would be the impact of our research results?

The research presented in this thesis contributes to precision medicine in paediatric oncology on two levels. The first study provides consolidated, moderate-certainty evidence supporting the routine use of antibiotic-impregnated ventriculoperitoneal shunts, reinforcing their role as a standard preventive intervention in paediatric

neurosurgery. This has direct implications for clinical guidelines, patient safety, and healthcare resource utilisation (11, 18).

The second study demonstrates the feasibility and clinical value of therapeutic drug monitoring for selumetinib in children with neurofibromatosis type 1. By identifying substantial interindividual variability in drug exposure and proposing a preliminary therapeutic range, it establishes a foundation for individualised dosing and future multicentre validation studies.

Together, these results highlight that precision medicine must extend beyond genomics to include prevention strategies and pharmacokinetic optimisation. By integrating population-level prevention with individualised treatment adjustment, this work supports a safer, more effective, and more patient-centred model of paediatric oncology care.

6. OBJECTIVES

6.1. Study I. – Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-analysis

The objective of this meta-analysis was to evaluate the effectiveness of antibiotic-impregnated shunt catheters in reducing the risk of shunt infection compared with conventional shunt catheters. Attention was given to paediatric patients, including infants younger than one year of age, who are known to be at the highest risk for shunt-related infections. In addition to infection outcomes, secondary endpoints such as shunt failure rates and healthcare costs were examined whenever sufficient data were available. Furthermore, the methodological quality of the included studies and the overall certainty of the evidence were critically assessed to provide a comprehensive and reliable evaluation of the current literature.

6.2. Study II. – Personalized Selumetinib Dosing in Paediatric NF1: Insights from a Pilot Therapeutic Drug Monitoring Study

The objectives of this study were to characterise the pharmacokinetic profile of selumetinib in Hungarian paediatric patients with neurofibromatosis type 1 (NF1) and plexiform neurofibromas, and to investigate the relationship between drug exposure, quantified by the area under the concentration–time curve (AUC), and the occurrence of treatment-related adverse events. The study also aimed to assess the extent of interindividual variability in selumetinib pharmacokinetics and to explore potential contributing factors, including sex, age, body mass index (BMI), and body surface area (BSA). Furthermore, a key objective was to propose a preliminary therapeutic AUC range that could support individualised dosing strategies. Finally, the feasibility and potential clinical utility of implementing therapeutic drug monitoring (TDM) in the management of paediatric patients receiving targeted therapy were evaluated.

7. METHODS

7.1. Study I.

7.1.1. Search Strategy and Study Selection

A systematic literature search was conducted across multiple databases, including PubMed, Embase, Scopus, and the Cochrane Library, from their inception to July 2023. The search combined controlled vocabulary terms and free-text keywords such as ventriculoperitoneal shunt, antibiotic-impregnated catheter, infection, and paediatric. Reference lists of relevant articles were also screened for additional eligible studies. The protocol was prospectively registered in the PROSPERO database (CRD42022370732) to ensure methodological transparency.

Eligible studies included randomised controlled trials (RCTs) and observational cohort studies comparing AISC with standard shunt catheters across all age groups. Studies were required to report infection rates or provide sufficient data to calculate infection risk ratios. Exclusion criteria included case reports, reviews, conference abstracts without full data, and studies with overlapping patient populations.

7.1.2. Data Extraction and Quality Assessment

Two reviewers independently screened titles, abstracts, and full texts for inclusion. Data were extracted using a standardised form capturing study characteristics (design, setting, sample size), patient demographics, infection definitions, follow-up duration, and outcomes. Risk of bias was evaluated using Cochrane RoB 2.0 for RCTs and Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) for observational studies (19, 20). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was applied to assess the overall certainty of evidence for the primary outcome (21).

7.1.3. Statistical Analysis

All statistical analyses were conducted using random-effects models to account for between-study heterogeneity. The primary effect measure was the odds ratio (OR) for infection comparing AISC with standard shunts. Heterogeneity was quantified using the

I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (22). Subgroup analyses were performed by age group, study design (RCT versus observational), and geographic region. Publication bias was assessed using funnel plots and Egger's regression test (23).

7.2. Study II.

7.2.1. Study Design and Setting

This single-centre observational pilot study was conducted at Semmelweis University in Budapest, under the coordination of the Paediatric Centre's Neuro-Oncology Working Group. Clinical care and sampling were performed at the Tűzoltó Street Unit, while pharmacokinetic analyses were carried out at the Institute of Laboratory Medicine's Mass Spectrometry Laboratory.

The study was approved by the Scientific and Research Ethics Committee of the Health Science Council (BM/13218-0/2023). Written informed consent was obtained from parents or legal guardians, and assent was secured from children when appropriate.

7.2.2. Participants

Twenty-two children aged 5–18 years with a confirmed molecular or clinical diagnosis of NF1 and radiologically verified plexiform neurofibromas were enrolled between autumn 2022 and spring 2024. All were receiving selumetinib (Koselugo) under routine clinical indications. Patients were eligible if they had achieved steady-state conditions after at least 1 month of continuous therapy and had no concurrent medications known to interact with CYP3A4 enzymes. Two additional NF1 patients provided clinical data without pharmacokinetic sampling.

The Semmelweis University Paediatric Centre manages approximately 80–90 % of Hungarian NF1 cases; thus, this cohort is highly representative of the national paediatric population receiving selumetinib.

7.2.3. Sampling Protocol

To obtain pharmacokinetic profiles, serial blood samples were collected during routine outpatient visits. One pre-dose sample (trough) and 5–7 post-dose samples over 0.25–8

hours were drawn via peripheral venous cannula into ethylenediaminetetraacetic acid (EDTA) tubes. Participants were instructed to fast before sampling and to avoid high-fat meals, given the potential effects of food on selumetinib absorption.

7.2.4. Analytical Quantification

Plasma concentrations were measured using liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS), an analytical gold standard for small-molecule quantification. The validated assay featured a lower limit of quantification of 1 ng/mL and demonstrated intra- and inter-assay precision within 10%.

Quality-control samples were analysed with each batch to ensure accuracy. Pharmacokinetic calculations—including apparent clearance (CL/F), half-life ($t_{1/2}$), and AUC—were performed using non-compartmental modelling with the NonCompart and ncar packages in R.

7.2.5. Clinical Assessment

Comprehensive clinical data were collected, including demographics, baseline PN characteristics, MRI-based tumour size, symptomatology, laboratory parameters, and treatment-related adverse events. Dose modifications, interruptions, and reasons for adjustment were documented.

7.2.6. Statistical Analysis

Descriptive statistics summarised patient characteristics and pharmacokinetic parameters. Differences between groups with and without side effects were assessed using non-parametric tests (Mann–Whitney U). Correlations between AUC and clinical variables were evaluated with Spearman's ρ . Statistical significance was set at $p < 0.05$.

8. RESULTS

8.1. Study I: Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-Analysis

8.1.1. Study Search and Selection

Our search key consists of three domains: ventriculoperitoneal-shunt, infection, and prophylaxis/treatment domain.

After conducting a thorough systematic search, the articles were imported into a reference management tool (EndNote 20.1, Clarivate). Automatic and manual processes were used to remove duplicate articles based on overlapping publication years, authors, and titles. Two reviewers independently conducted screening and selection, initially focusing on title and abstract, and subsequently on full-text evaluation to ensure eligibility criteria were met. Cohen's kappa coefficient was calculated at both stages of selection to assess inter-reviewer reliability. (Figure 1.)

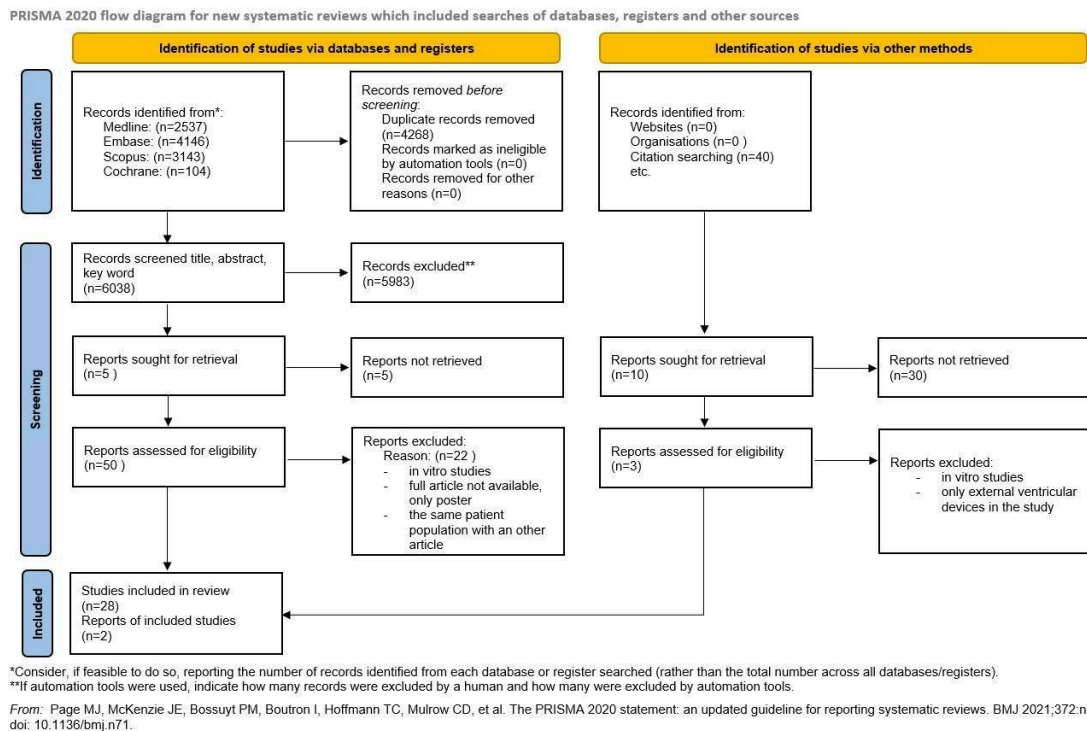


Figure 1. PRISMA flowchart of the article selection process

Table 1. Basic characteristics of the included studies

First Author and year of publication		Study design	Mean age + SD/Range	Population details	Number of procedures (AISC/non-AISC)	Number of infections
Mallucci et al. ⁽¹¹⁾	2019	multi-centre, single-blinded, randomised trial	42.5 years; Range:0.8–69.6 years	all patients	Total: 1068 (535/533)	Total: 12/535 vs. 32/533
Ritz et al. ⁽²⁴⁾	2007	observational study	AIS: 32.8 years standard: 42.4 years	all patients	Total: 258 (86/172)	Total: 5/86 vs. 10/172
Raffa et al. ⁽²⁵⁾	2015	retrospective case-control study	AIS: 61.59 days; Range: preterms - 300 days standard: 70.46 days; Range: preterms - 360 days	neonates (under one year old)	Total: 48 (22/26)	Total: 2/22 vs. 9/26
Jaeger et al. ⁽²⁶⁾	2017	retrospective study	AIS: 15 days; Range:2–114 days standard: 15 days; Range:1-110 days	neonates (younger than 28 days), corrected age	Total: 47 (23/24)	Total: 2/23 vs. 5/24
Gonzalez et al. ⁽²⁷⁾	2011	retrospective	43.7 years SD: 26.2	all patients	Total: 231 (119/112)	Total: 8/119 vs. 21/112
Sciubba et al. ⁽²⁸⁾	2007	retrospective study	AIS: 3 years; Range:1-11 years	children	Total: 353 (145/208)	Total: 2/145 vs. 25/208

First Author and year of publication		Study design	Mean age + SD/Range	Population details	Number of procedures (AISC/non-AISC)	Number of infections
			standard: 10 years; range: 2-16 years			
Gonzalez et al. ⁽²⁹⁾	2010	retrospective study	NA	all patients	Total: 119 (72/47)	Total: 2/72 vs. 8/47
Parker et al. ⁽³⁰⁾	2015	retrospective longitudinal analysis	AIS: 64.4 years SD:18.0 standard: 62.5 years SD: 17.7	all patients, excluding neonates	Total: 12589 (1192/11397)	Total: 12/1192 vs. 469/11397
Parker et al. ⁽³¹⁾	2011	retrospective study	60 years SD: 18	adult patients	Total: 500 (250/250)	Total: 3/250 vs. 10/250
Eymann et al. ⁽³²⁾	2008	retrospective study	AIS: 71.3 years SD:9.2 standard: 70.0 years SD: 12.9	all patients	Total: 317 (197/120)	Total: 2/197 vs. 9/120
Govender et al. ⁽³³⁾	2003	prospective, randomised, blind study	Range: 1 month to 72 years	all patients	Total: 110 (50/60)	Total: 3/50 vs. 10/60
James et al. ⁽³⁴⁾	2014	single-centre, retrospective study	3.9 years; Range: 0-17 years	0-17 years old patients	Total: 2092 (500/1592)	Total: 25/500 vs. 135/1592
Pattavilakom et al. ⁽³⁵⁾	2007	prospective study	NA	all patients	Total: 794 (243/551)	Total: 3/243 vs. 36/551
Richards et al. ⁽³⁶⁾	2009	registry analyses	NA	all patients	Total: 1988 (994/994)	Total: 30/994 vs. 47/994

First Author and year of publication		Study design	Mean age + SD/Range	Population details	Number of procedures (AISC/non-AISC)	Number of infections
Aryan et al. ⁽³⁷⁾	2005	retrospective study	4.5 years; Range: 6 months to 17 years	children	Total: 78 (32/46)	Total: 1/32 vs. 7/46
Kan et al. ⁽³⁸⁾	2007	retrospective study	AIS: 7.9 years, standard: 6.8 years	children	Total: 160 (80/80)	Total: 4/80 vs. 7/80
Hayhurst et al. ⁽³⁹⁾	2007	retrospective analyses	Range: 1 day to 16 years	children	Total: 335 (247/88)	Total: 24/247 vs. 11/88
Parker et al. ⁽¹⁸⁾	2008	retrospective study	6.5 years; Range: 1 day to 20 years	children	Total: 1009 (502/507)	Total: 16/502 vs. 64/507
Kandasamy et al. ⁽⁴⁰⁾	2011	retrospective study, 3 centre	Range: 1 day to 16 years	children <16 years	Total: 2544 (581/1963)	Total: 30/581 vs. 155/1963
Yang et al. ⁽⁴¹⁾	2016	retrospective study	AIS: 17.1 months Range: 3 months-4 years; standard: 13.7 months Range: 1 month-3.2 years	children	Total: 1543 (974/569)	Total: 17/974 vs. 28/569
Sorar et al. ⁽⁴²⁾	2014	retrospective study	33.6 months SD:43.3	children	Total: 211 (18/193)	Total: 0/18 vs. 12/193
Albanese et al. ⁽⁴³⁾	2009	retrospective study	62.8 years SD:13.1	adults with high risk (severely disabled)	Total: 13 (6/7)	Total: 0/6 vs. 7/7

First Author and year of publication		Study design	Mean age + SD/Range	Population details	Number of procedures (AISC/non-AISC)	Number of infections
Attenello et al. ⁽⁸⁾	2009	retrospective study	7 years; Range: 2 weeks-18 years	children	Total: 608 (400/208)	Total: 13/400 vs. 25/208
Wong et al. ⁽¹⁰⁾	2010	prospective randomised trial	AIS: 53 years SD:14 standard: 51 years SD: 14	adults	Total: 184 (90/94)	Total: 51/90 vs. 48/94
Mbabazi-Kabach elor et al. ⁽⁴⁴⁾	2019	single-blind, RCT	AIS: 8.4 months SD:11.4 standard: 7.4 months SD: 9.5	children younger than 16 years	Total: 248 (124/124)	Total: 6/124 vs. 8/124
Lane et al. ⁽⁴⁵⁾	2014	retrospective cohort study	AIS: 9.7 months SD: 17.1 standard: 12.9 months SD: 18.1	children	Total: 160 (80/80)	Total: 4/80 vs. 11/80
Steinbok et al. ⁽⁴⁶⁾	2010	prospective, multicentre, noncontrolled, open-label registry	31.3 years; Range: 0-86 years	all patients	Total: 433 (46/387)	Total: 0/46 vs. 14/387

SD: Standard Deviation; AISC: Antibiotic-Impregnated Shunt Catheter; NA: Not Available

8.1.2. Primary Outcomes

A total of 27 studies comprising 27,266 shunt operations were included. The studies were conducted across Europe, North America, and Asia, encompassing both adult and paediatric populations, though most reported substantial paediatric representation. The proportion of infants (<1 year) varied from 10% to 60% among paediatric cohorts.

The most used antibiotic combination was rifampicin and clindamycin, though some studies used minocycline and rifampicin. Follow-up durations ranged from 3 months to 3 years, with infection definitions typically based on positive CSF cultures or clinical criteria requiring shunt removal.

The pooled analysis demonstrated that AISC significantly reduced the risk of shunt infection compared with standard catheters (OR: 0.42; 95% CI 0.30–0.58). This represents an approximate 58% reduction in infection risk. The result was consistent across both RCTs and observational cohorts. (Figure 2)

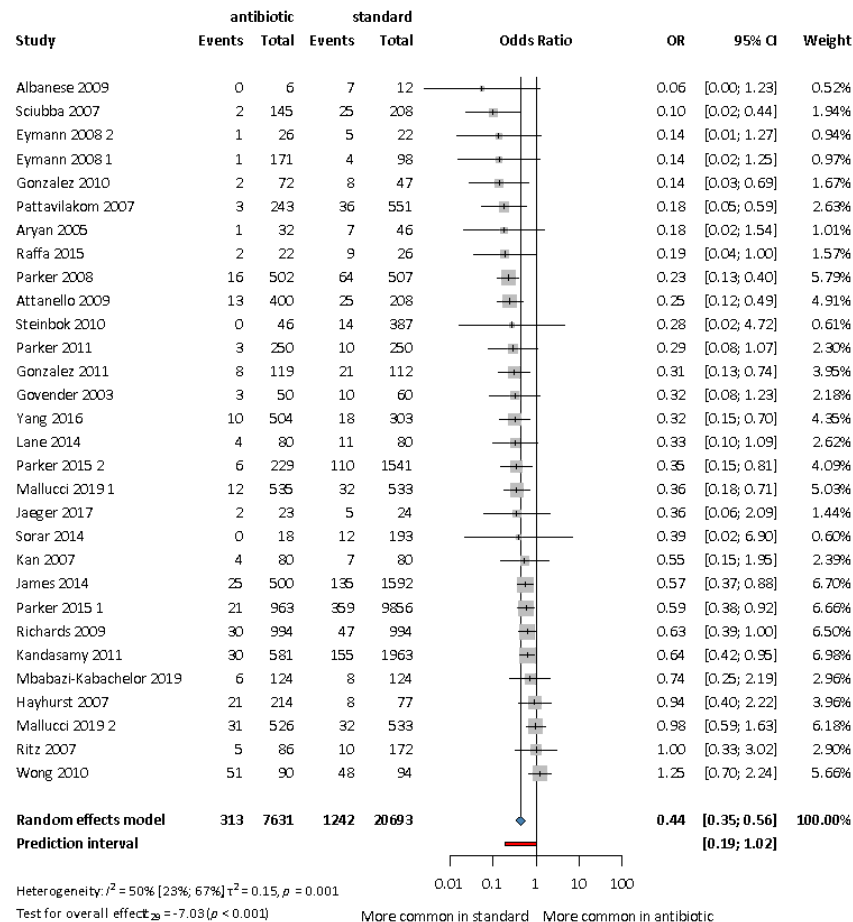


Figure 2. Forest plot demonstrating the anti-bacterial effect of the antibiotic-impregnated shunts compared to standard shunts. OR: odds ratio, CI: confidence interval

Subgroup Analyses

Paediatric patients: The protective effect of AISC was more pronounced in children compared to mixed-age cohorts, highlighting the particular benefit of antibiotic impregnation in this vulnerable group.

Infants (<1 year): Among infants, the infection reduction was even more striking, with an odds ratio 0.32. (Figure 3)

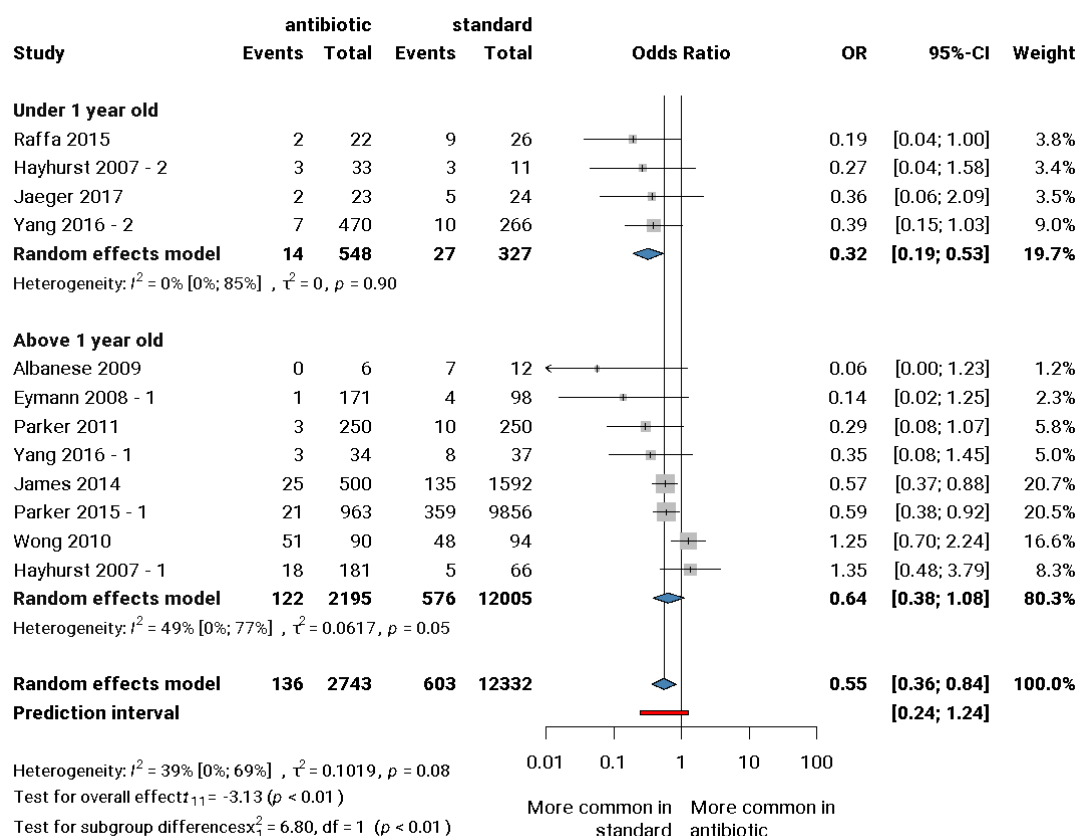


Figure 3. Forest plot demonstrating the anti-bacterial effect of the antibiotic-impregnated shunts compared to standard shunts in age-based subgroups. OR: odds ratio, CI: confidence interval

8.1.3. Secondary Outcomes

While data on shunt failure and cost-effectiveness were limited, some studies reported a trend toward improved shunt survival and lower overall healthcare costs with AISC, driven by fewer infection-related revisions (30, 34, 40). However, the pooled results for shunt failure did not reach statistical significance with 0.73 OR (CI: 0.51; 1.06), likely due to heterogeneity and insufficient data. (Figure 4)

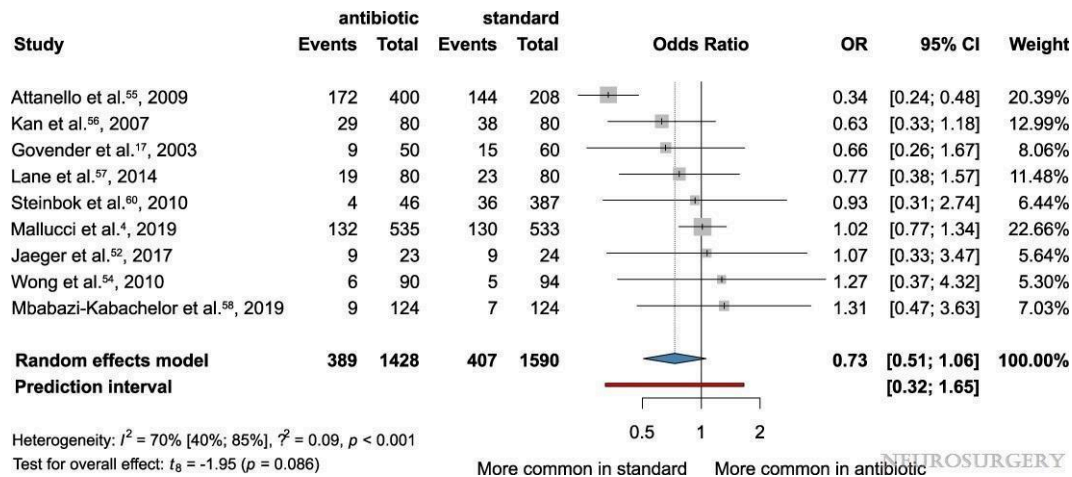


Figure 4. Forest plot demonstrating the rate of shunt failure of the antibiotic-impregnated shunts compared to standard shunts. OR: odds ratio, CI: confidence interval

8.1.4. Risk of Bias Assessment and Quality of Evidence

The risk of bias was generally low to moderate (Figures 5 and 6). The certainty of evidence for infection reduction was rated as moderate according to GRADE, downgraded mainly due to study heterogeneity and reliance on observational data. Nevertheless, the consistency and magnitude of effect lend strong support to the clinical relevance of AISC.

		Risk of bias domains							
		D1	D2	D3	D4	D5	D6	D7	Overall
Study	Albanese et al ⁴⁷ , 2009	+	+	+	+	+	-	+	-
	Aryan et al ⁴⁴ , 2005	+	+	-	+	+	-	+	×
	Attenello et al ⁵⁵ , 2009	+	+	+	+	+	-	+	-
	Eymann et al ⁷ , 2008	+	+	+	+	+	-	+	-
	Gonzalez et al ⁴⁰ , 2011	+	+	+	+	+	-	+	-
	Gonzalez et al ¹² , 2010	+	+	-	-	+	-	+	×
	Hayhurst et al ⁴⁹ , 2007	-	+	+	-	+	-	+	×
	Jaeger et al ⁵² , 2017	-	+	+	-	+	-	+	×
	James et al ⁵³ , 2014	-	+	+	-	+	-	+	×
	Kan et al ⁵⁶ , 2007	+	+	+	+	+	-	+	-
	Kandasamy et al ⁴⁶ , 2011	-	+	+	-	+	-	+	×
	Lane et al ⁵⁷ , 2014	+	+	+	-	-	-	+	×
	Parker et al ⁴⁵ , 2008	+	+	+	-	+	-	+	×
	Parker et al ⁴⁸ , 2015	+	-	+	-	+	-	+	×
	Pattavilakom et al ¹⁶ , 2007	-	+	+	-	+	-	+	×
	Raffa et al ⁵⁰ , 2015	+	+	+	-	+	-	+	×
	Richards et al ⁴³ , 2009	+	-	+	-	-	-	+	×
	Ritz et al ⁴¹ , 2007	+	+	-	+	-	-	+	×
	Sciubba et al ⁴² , 2007	+	-	+	-	+	-	+	×
	Sorar et al ⁵⁹ , 2014	+	-	+	-	+	-	+	×
	Steinbok et al ⁶⁰ , 2010	+	+	-	-	+	-	+	×
	Yang et al ⁵¹ , 2016	+	-	+	+	+	-	+	×

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement

⊗ Serious

⦿ Moderate

⊕ Low

Figure 5. Risk of bias assessment for the observational studies

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Govender et al ¹⁷ , 2003						
	Mbabazi-Kabachelor et al ⁵⁸ , 2019						
	Mallucci et al ⁴ , 2019						
	Wong et al ⁵⁴ , 2010						

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
 High
 Some concerns
 Low
 No information

Figure 6. Risk of bias assessment for the randomised controlled trials

8.2. Study II: Personalized Selumetinib Dosing in Paediatric NF1: Insights from a Pilot Therapeutic Drug Monitoring – Observational Study

8.2.1. Study Population and Treatment Characteristics

The study cohort consisted of 22 paediatric patients diagnosed with NF1-associated plexiform neurofibromas. The sex distribution was balanced, with 11 girls and 11 boys enrolled. The median age at pharmacokinetic sampling was 12 years (range: 5–18 years).

All patients had radiologically confirmed plexiform neurofibromas and were receiving selumetinib treatment according to routine clinical practice. The anatomical distribution of tumours was heterogeneous and included lesions involving the head and neck region, trunk, paraspinal areas, and extremities. The most frequent clinical indications for treatment initiation were tumour-related pain, functional impairment, progressive tumour growth, and cosmetic disfigurement.

Most patients presented with additional manifestations of NF1, including multiple café-au-lait macules and cutaneous neurofibromas. Baseline clinical and laboratory assessments did not identify contraindications to selumetinib treatment, and all patients successfully completed pharmacokinetic sampling.

All patients received selumetinib according to the approved body-surface-area-based dosing regimen. During therapy, dose modifications were occasionally required due to treatment-related adverse events. Temporary treatment interruptions were more common than permanent dose reductions and typically occurred during the first months of therapy.

The duration of therapy before pharmacokinetic assessment varied among participants; however, all patients had achieved steady-state conditions at the time of sampling. No patient discontinued therapy before pharmacokinetic evaluation.

8.2.2. Primary Outcomes

Clinical outcomes were generally favourable. Stable disease represented the most common treatment response and was observed in 18 patients (75%). One patient (4.1%) achieved partial tumour regression during follow-up, while three patients (12.5%) demonstrated slow radiological progression despite treatment.

In addition to radiological outcomes, several patients reported subjective clinical improvement, including reduced pain intensity, improved mobility, and decreased tumour-related discomfort. Although these parameters were not formally quantified, they contributed substantially to the overall clinical benefit observed during treatment.

Treatment-related adverse events occurred in 14 patients (63.6%). The most commonly observed toxicities included dermatological manifestations and elevations of serum creatine kinase levels. Most adverse events were manageable with supportive measures and dose adjustment strategies.

Five patients required permanent dose reduction because of toxicity, whereas temporary treatment interruptions were implemented more frequently. No treatment-related deaths or unexpected severe toxicities were observed during the study period.

8.2.3. Pharmacokinetic Findings

Pharmacokinetic analysis revealed marked interindividual variability despite standardised dosing based on body surface area. Considerable differences were observed in dose-normalised exposure values, indicating that patients receiving similar nominal doses could experience substantially different systemic drug concentrations.

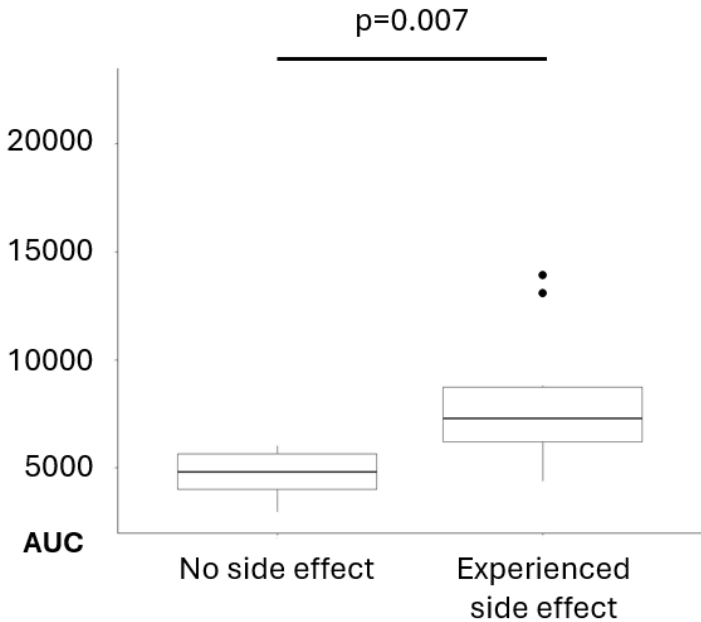
Among patients who achieved stable disease, those experiencing treatment-related adverse events generally demonstrated higher dose-normalised AUC values than patients without toxicity. Those with side effects ($n = 10$) exhibited higher AUCs (range 4374–13 923 nmol*h/L). Those without side effects ($n = 8$) had lower AUCs (range 2961–6011 nmol*h/L). The observed separation between groups suggested a potential

exposure–toxicity relationship, although overlap among individual measurements persisted.

One patient without clinically significant adverse events demonstrated an exceptionally high exposure value ($AUC = 22,512 \text{ nmol}\cdot\text{h/L}$), substantially exceeding the range observed in other participants. Because this observation represented a clear outlier and had a disproportionate effect on summary statistics, graphical presentation of exposure distributions was performed both including and excluding this individual case.

Correlation analyses did not demonstrate statistically significant associations between dose-normalised AUC and demographic or anthropometric variables, including age, sex, BMI, and BSA. These findings suggest that commonly used clinical parameters may not adequately explain the pharmacokinetic variability observed during selumetinib treatment.

Based on the subgroup of patients who achieved stable disease without clinically



relevant adverse events, a preliminary therapeutic exposure range of 2961–6011 $\text{nmol}\cdot\text{h/L}$ was proposed. This range was derived from real-world pharmacokinetic observations and may serve as a basis for future validation studies investigating

exposure-guided dosing strategies. (Figure 7)

Figure 7. Dose-Normalised area under the concentration-time curve (AUC) in $\text{nmol}\cdot\text{h/L}$ in Stable Disease Patients (n=19) by Adverse Event Status without the outlier

9. DISCUSSION

9.1. Summary of Findings, International Comparisons

This thesis addresses two complementary dimensions of precision medicine in paediatric care: prevention of avoidable complications and individualisation of therapy. Although the studies focus on different clinical settings, paediatric neurosurgery and paediatric oncology, they converge on a shared objective: improving safety and outcomes through evidence-based, patient-specific strategies.

The first study provides comprehensive quantitative evidence that antibiotic-impregnated ventriculoperitoneal shunt catheters significantly reduce shunt-related infections, particularly in paediatric and infant populations. The magnitude of effect observed is consistent with international reports from Europe, North America, and Australia, supporting the biological rationale that local antimicrobial release prevents early bacterial adherence and biofilm formation (11, 31, 34, 40). Compared with earlier heterogeneous single-centre studies, this meta-analysis offers a more robust estimate of benefit and confirms that the protective effect of antibiotic-impregnated shunts is generalizable across healthcare systems.

The second study represents one of the first real-world pharmacokinetic evaluations of selumetinib in children with neurofibromatosis type 1 (1, 47, 48). It demonstrates substantial interindividual variability in drug exposure despite standardised body surface area-based dosing and identifies a clear association between higher exposure and increased toxicity. These findings align with emerging international pharmacometrics data on MEK inhibitors but extend the literature by providing empirical paediatric exposure data that were not systematically assessed in pivotal clinical trials such as SPRINT (1, 47, 48). Together, the results support therapeutic drug monitoring as a clinically relevant tool for optimising targeted therapy in paediatric oncology (49).

Taken together, both studies highlight that precision medicine in paediatrics must address not only molecular targets but also preventable risks and pharmacokinetic variability, reinforcing a broader, more pragmatic interpretation of individualised care.

9.2. Strengths

A major strength of this thesis is the complementary methodological approach across studies. The meta-analysis leverages a large cumulative sample size and rigorous synthesis of evidence to overcome the limitations of underpowered individual studies, enhancing the reliability and clinical relevance of its conclusions. The consistency of findings across diverse study designs and international settings supports their external validity.

The pharmacokinetic pilot study, although smaller in scale, offers high clinical relevance by providing real-world data in a paediatric population that is underrepresented in pharmacokinetic research. The use of validated LC-MS/MS assays, clinically feasible sampling strategies, and exposure–toxicity analysis strengthens the translational value of the findings. Importantly, the study demonstrates that therapeutic drug monitoring can be integrated into routine paediatric oncology workflows.

An additional strength lies in the conceptual integration of prevention and personalisation. By addressing both device-related infection risk and drug-related toxicity, this thesis presents a holistic view of precision medicine that is directly applicable to everyday paediatric clinical practice.

9.3. Limitations

Several limitations should be acknowledged. In the meta-analysis, heterogeneity in infection definitions, perioperative protocols, and follow-up duration likely contributed to residual variability. The lack of blinding in most included studies may introduce bias, although the objective nature of microbiologically confirmed infections mitigates this concern. Data on long-term outcomes beyond the initial antibiotic release period remain limited.

The pharmacokinetic study is constrained by its pilot design, including a small sample size, a single-centre setting, and incomplete control of factors such as fasting status and adherence. The absence of formal toxicity grading limited detailed exposure–response

modelling. As a result, the proposed therapeutic range should be interpreted as preliminary and requires validation in larger, multicentre cohorts.

Despite these limitations, both studies provide biologically plausible, internally consistent findings that justify further investigation. Together, they lay the groundwork for future research integrating infection-prevention strategies and pharmacokinetic optimisation into standardised paediatric care pathways.

10. CONCLUSIONS

10.1. Study I. – Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-Analysis

Antibiotic-impregnated ventriculoperitoneal shunt catheters were associated with a significantly lower risk of shunt-related infections compared with conventional catheters. The protective effect was particularly evident in paediatric patients and infants. These findings support the routine use of antibiotic-impregnated shunts as an effective infection-prevention strategy in paediatric neurosurgery.

10.2. Study II. – Personalized Selumetinib Dosing in Paediatric NF1: Insights from a Pilot Therapeutic Drug Monitoring Study

Substantial interindividual variability in selumetinib exposure was observed despite standardised body-surface-area-based dosing. Higher drug exposure appeared to be associated with an increased risk of treatment-related adverse events, while conventional patient characteristics did not adequately explain the observed variability. These findings support the feasibility and potential clinical value of therapeutic drug monitoring for individualised selumetinib dosing in paediatric patients with neurofibromatosis type 1.

11. IMPLICATIONS FOR PRACTICE

The findings of this thesis have direct, actionable implications for paediatric clinical practice, particularly in neurosurgery and oncology, and support broader integration of precision-based approaches into routine care.

In paediatric neurosurgery, the demonstrated effectiveness of antibiotic-impregnated ventriculoperitoneal shunt catheters supports their routine use, especially in infants and high-risk paediatric populations. Given the substantial reduction in shunt-related infections and the associated clinical and economic benefits, antibiotic-impregnated shunts should be considered a standard component of infection-prevention strategies. Their implementation is particularly relevant in resource-limited settings, where preventing shunt infections can significantly reduce the burden of repeated surgeries, prolonged hospitalisation, and long-term neurological morbidity.

In paediatric oncology, observed interindividual variability in selumetinib exposure underscores the limitations of body-surface-area-based dosing for oral targeted therapies. The feasibility of therapeutic drug monitoring demonstrated in this thesis supports its incorporation into clinical management for children with neurofibromatosis type 1 receiving selumetinib. Measuring drug exposure enables clinicians to identify patients at risk of toxicity or subtherapeutic dosing and to individualise treatment, accordingly, improving both tolerability and efficacy.

More broadly, this work underscores the importance of integrating pharmacokinetic expertise and laboratory-based monitoring into paediatric oncology care pathways. Establishing multidisciplinary collaboration between clinicians, pharmacologists, and laboratory specialists is essential for the successful implementation of therapeutic drug monitoring and may serve as a model for other targeted agents entering paediatric practice.

Finally, the combined findings emphasise that precision medicine in paediatrics must extend beyond molecular diagnostics. Evidence-based prevention of device-related complications and pharmacokinetically guided therapy adjustment represent practical,

immediately applicable strategies for improving patient safety and quality of care. Adoption of such approaches can contribute to more rational, efficient, and patient-centred paediatric healthcare.

12. IMPLICATIONS FOR RESEARCH

12.1. Methodology and Study Design

The findings of this thesis highlight the importance of methodological rigour and appropriately tailored study designs in paediatric precision medicine research. The meta-analysis demonstrates the value of systematic evidence synthesis in consolidating heterogeneous clinical data and informing practice where RCTs are limited or impractical. Future research on infection prevention in paediatric neurosurgery should prioritise multicentre, paediatric-focused RCTs with standardised definitions of infection, uniform perioperative protocols, and sufficiently long follow-up to capture both early and late outcomes.

The pharmacokinetic pilot study underscores the need for incorporating pharmacokinetic and pharmacodynamic endpoints into clinical trials of targeted therapies in children. Traditional efficacy-focused trial designs may overlook clinically relevant exposure–response relationships. Future studies should integrate therapeutic drug monitoring, sparse sampling strategies, and population pharmacokinetic modelling to better characterise interindividual variability. Multicentre collaboration will be essential to achieve adequate sample sizes in rare paediatric conditions such as neurofibromatosis type 1.

Additionally, both studies illustrate the importance of real-world data in complementing controlled trial results. Pragmatic study designs embedded in routine clinical care can provide valuable insights into feasibility, adherence, and implementation barriers, which are critical for translating research findings into practice

12.2. New Areas

This thesis identifies several new avenues for future research. In paediatric neurosurgery, further investigation into next-generation shunt technologies, including non-antibiotic antimicrobial coatings and combination infection-prevention strategies, is warranted. Implementation science approaches should be applied to evaluate barriers and facilitators to the adoption of antibiotic-impregnated shunts across diverse healthcare settings, particularly in low- and middle-income countries.

In paediatric oncology, the results support expanding therapeutic drug monitoring research to other oral targeted agents with narrow therapeutic windows and high pharmacokinetic variability. Integrating pharmacogenomic data with pharmacokinetic monitoring represents a promising direction for refining individualised dosing algorithms. Longitudinal studies are also needed to assess how pharmacokinetic optimisation influences long-term outcomes, including tumour control, quality of life, and neurodevelopment.

More broadly, the integration of prevention-focused and pharmacokinetic-guided research underscores the need for interdisciplinary studies that bridge surgery, oncology, pharmacology, and health economics. Such approaches will be central to advancing a comprehensive precision medicine framework that improves safety, effectiveness, and sustainability of paediatric healthcare.

13. IMPLICATIONS FOR POLICY MAKERS

The findings of this thesis support greater integration of prevention-oriented and precision-based approaches into paediatric healthcare systems. The significant reduction in shunt infections associated with antibiotic-impregnated shunts suggests that their broader implementation could improve patient safety and reduce healthcare costs associated with repeated surgeries and prolonged hospitalisation.

In addition, the observed variability in selumetinib exposure highlights the need for healthcare systems to support therapeutic drug monitoring and individualised dosing strategies for targeted therapies in children. Policymakers should encourage the development of multidisciplinary precision medicine programs that integrate clinical care, pharmacology, and laboratory monitoring.

Overall, investment in preventive technologies and personalised treatment approaches may contribute to more effective and more sustainable paediatric healthcare.

14. FUTURE PERSPECTIVES

The future of paediatric oncology and neurosurgery will increasingly be shaped by precision-based strategies that integrate prevention, pharmacokinetic optimisation, and multidisciplinary collaboration. As therapeutic and technological complexity grows, the systematic reduction of preventable harm will remain a central priority alongside improvements in efficacy.

In paediatric neurosurgery, future developments are likely to focus on refining infection-prevention strategies. Advances in biomaterials, including non-antibiotic antimicrobial coatings and smart implant technologies, may enhance protection while addressing concerns related to antimicrobial resistance. The integration of such innovations with standardised surgical bundles, real-time infection surveillance, and quality-improvement frameworks has the potential to significantly reduce shunt-related infections across diverse healthcare settings.

In paediatric oncology, the expanding use of oral targeted therapies will necessitate a transition from fixed-dosing paradigms to adaptive, exposure-guided treatment strategies. Therapeutic drug monitoring, supported by population pharmacokinetic modelling and pharmacogenomic profiling, is expected to play an increasingly important role in optimising drug exposure and minimising toxicity. As analytical methods become more accessible, real-time dose adjustment based on individual pharmacokinetic data may become part of routine clinical care.

At a broader level, future progress will depend on integrating clinical, pharmacokinetic, genomic, and health system data into learning healthcare systems. Such systems enable continuous feedback between research and practice, facilitating rapid translation of evidence into improved patient care. Multidisciplinary collaboration among clinicians, pharmacologists, laboratory scientists, and health system stakeholders will be essential to realize this vision.

Ultimately, the future perspective emerging from this work is one in which precision medicine in paediatrics extends beyond molecular targeting to encompass prevention,

monitoring, and individualised adaptation at every stage of care. This comprehensive approach holds promise for improving not only survival but also long-term quality of life for children facing complex medical conditions.

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16.1. Publications Related to the Thesis

Kovács, Janka; Máté, Vanda; Obeidat, Mahmoud; Nagy, Rita; Agócs, Gergely; Kiss-Dala, Szilvia; Hegyi, Péter; Kiss-Miki, Renáta; Párniczky, Andrea; Müller, Katalin E. et al (2024) Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-Analysis **NEUROSURGERY** 95:6 pp. 1263-1273., 11 p.

D1, IF: 5

Janka Kovács; Zoltán Köllő; Balázs Gellért Karvaly; Mahmoud Obeidat; Rita Nagy; Péter Hegyi; Brigitta Teutsch; Eszter Tuboly; Miklós Garami; Personalized Selumetinib Dosing in Pediatric Neurofibromatosis Type 1: Insights From a Pilot Therapeutic Drug Monitoring Study **PEDIATRIC BLOOD AND CANCER**

Q1, IF: 2.3

16.2. Publications not Related to the Thesis

Kollo, Zoltan; **Kovacs, Janka**; Neely, Michael N.; Vasarhelyi, Barna; Bruckner, Edit; Szabo, Attila J.; Garami, Miklos; Karvaly, Gellert Balazs (2025) A Nonparametric Population Pharmacokinetic Model of Selumetinib in Pediatric Patients Diagnosed With Neurofibromatosis-I or Plexiform Neurofibromas **CPT: PHARMACOMETRICS AND SYSTEMS PHARMACOLOGY**, 12 p.

Q1, IF: 3

Kovács, Janka; Köllő, Zoltán; Karvaly, Gellért Balázs; Garami, Miklós (2024) Terápiás gyógyszer-szint-monitorozás a protein-kinázokkal végzett gyermekonkológiai kezelések során: a selumetinib-expozíció egyének közötti jelentős eltérései **ONKOLÓGIA & HEMATOLÓGIA: AZ ONCOLOGY FOLYÓIRAT MAGYAR NYELVŰ KIADÁSA** 14:4 pp. 15-17., 3 p.

NO IF.

Kovács, Janka; Máté, Vanda; Obeidat, Mahmoud; Nagy, Rita ; Agócs, Gergely; Kiss-Dala, Szilvia; Hegyi, Péter; Kiss-Miki, Renáta; Párniczky, Andrea; Müller, Katalin E et al. (2024) In Reply: Antibiotic-Impregnated Ventriculoperitoneal Shunts Decrease Bacterial Shunt Infection: A Systematic Review and Meta-Analysis **NEUROSURGERY** 95:5 pp. e145-e148., 4 p.

D1, IF: 5

Kiss-Miki, Renáta; Obeidat, Mahmoud; Máté, Vanda; Teutsch, Brigitta; Agócs, Gergely; Kiss-Dala, Szilvia; Hegyi, Péter; **Kovács, Janka**; Párniczky, Andrea; Tuboly, Eszter et al. (2025) Proton or photon? Comparison of survival and toxicity of two radiotherapy modalities among pediatric brain cancer patients: A systematic review and meta-analysis

PLOS ONE 20:2 Paper: e0318194, 18 p.

Q1, IF: 2.6

Garami, Miklós; Juhász, Orsolya; **Kovács, Janka**; Szabados, Márton; Botos, Péter; Jakab, Zsuzsanna; Brückner, Edit (2025) Magas kockázatú neuroblastoma: nemzetközi kezelési protokollok és új terápiás lehetőségek **GYERMEKORVOS TOVÁBBKÉPZÉS** 24:3 pp. 160-164., 5 p.

NO IF.

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