Shaping the pharmacokinetic landscape for renally cleared antibiotics in obesity: Studies in adults, adolescents and children

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Part I

Introduction and background

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Introduction

SCOPE

A 45-year-old patient is admitted to the ICU with a life-threatening bloodstream infection. Treatment with intravenous antibiotics is immediately started. However, this specific patient is unlike any other: the patient is not only severely ill, but also weighs 165 kg, needs to be mechanically ventilated and is being treated with multiple vasoconstrictive agents to maintain blood pressure. Moreover, the lab results show that the patient's kidneys are failing. The medical team knows that the antibiotic treatment might save the patient's life, but could also result in serious side effects in case of overdose which might actually worsen the patient`s situation. Given the high body weight and kidney failure, how do we know that the prescribed dose will lead to an effective, but not toxic treatment in this particular individual?

This question is central to the scientific field of pharmacometrics, with pharmacokinetics (PK) and pharmacodynamics (PD) as primary domains. Pharmacokinetics (derived from the Greek *pharmakon* or `drug` and *kinetikos* or `movement`) is the study of the time course of drug absorption, distribution, metabolism and elimination, also referred to as ADME. How the drug exposure subsequently translates to an effect (for example a drop in blood pressure or pain relieve) is studied in the field of pharmacodynamics (*dynamikos* in Greek means `power`).

In the case of the discussed ICU patient, there are multiple factors that can influence a drug`s pharmacokinetics that need to be accounted for when dosing the right dose for the antibiotic. First, it is important to consider the fact that the patient is morbidly obese. Often drugs are dosed with a 'one-size-fits-all' fixed dose. It is however common for this antibiotic to 'individualize' the dose by dosing on body weight (in mg/kg). But can we use 165 kg as a dosing weight in our patient or should this be adjusted, and if so, how must we adjust the dose? How does the disposition of the drug change in an obese individual? As it is primary renally eliminated, we need to know how these processes change in obese patients. In addition, the patient`s deteriorating kidney function needs to be accounted for in selecting the dose. Lastly, we should consider the fact that our patient is also critically ill, and hemodynamically unstable for which ICU treatment is necessary, which can have additional effects on a drug`s pharmacokinetics.

The work presented in this thesis aims to provide answers to these issues. How should renally cleared drugs be dosed in obesity, especially in obese individuals who are renally impaired and/or critically ill? We have conducted studies to investigate the pharmacokinetics of renally cleared drugs in adult, adolescent and paediatric patients who are obese, renally impaired and/or critically ill. In these studies, we focus on the widely used antibiotics gentamicin, tobramycin and vancomycin, which are primary examples of the group of renally cleared (antibiotic) drugs that are used for severe infections.

GENTAMICIN, TOBRAMYCIN AND VANCOMYCIN

The 'antibiotic era', roughly from 1910 to 1970, commenced by the discovery of the antisyphilic antibiotic arsphenamine in 1909, by Paul Erlich and Sahachiro Hata [1]. During this period, discoveries of new classes of antibiotic drugs followed one another, with Alexander Fleming's serendipitous discovery of penicillin in 1929 as probably the most well-known example [2]. Three major events mark prominent highlights of the antibiotic era: the introductions of the aminoglycosides gentamicin, tobramycin and the glycopeptide antibiotic vancomycin.

In 1943, streptomycin was discovered as the first agent of the aminoglycoside class, a potent group of natural and semisynthetic antibiotics active against a wide range of both gram-positive and gram-negative bacteria [3]. This was later followed by introduction of less toxic aminoglycosides such as gentamicin (1963), tobramycin (1967) and the semisynthetic amikacin (1972) [4]. They inhibit bacterial growth by binding to ribosomes, essential organelles for protein synthesis and are especially synergistic in combination with other antimicrobial drugs. Because of a poor absorption from the gastrointestinal tract, aminoglycosides are usually administered parenterally [4]. With their low molecular weight (both around 470 g/mol) and hydrophilic properties, they easily penetrate intro interstitial fluid of different organ tissues. This makes them suitable for both empirical and directed treatment of a wide variety of (severe) infections, such as sepsis, endocarditis, intra-abdominal or urinary tract infections [4–6]. Gentamicin and tobramycin are renally cleared, with 81 – 88% of the administered drug being recovered in the urine in the first 24 hours [5]. In the first decades after their discovery, when the daily aminoglycoside dose was divided over multiple administrations, their use was complicated by nephro- and ototoxicity. To provide a better efficacy-toxicity balance, extension of the drug interval was investigated. Such an extension was possible given the fact that aminoglycosides possess a prolonged post-antibiotic effect, i.e. the period after complete removal of the drug during which there is no bacterial growth. Indeed, in 1993, a once daily regimen of gentamicin was shown to be less nephrotoxic and equally effective compared to a more frequent dosing schedule [7].

Another important discovery in the 'antibiotic era' was the isolation of the glycopeptide antibiotic vancomycin in 1958 [8]. Vancomycin inhibits bacterial cell growth by binding to the D-Ala-D-Ala dipeptide terminus of peptidoglycan precursors, thereby inhibiting cross-linking of peptidoglycan in the bacterial cell wall. This lack of cross-linking reduces the integrity of the cell wall, resulting in bacterial death [9]. Its antibacterial spectrum includes most gram-positive organisms, including penicillin-resistant *Staphylococci*, which is an emerging problem since the 1950s [10]. Nowadays, it is mainstay treatment for various severe infections with gram-positive organisms, including bacteraemia, endocarditis or osteomyelitis. However, given its high molecular weight (~ 1400 g/mol) tissue penetration is moderate and shows large

variability [8,11]. Vancomycin has a short half-life of 3 – 9 hours in healthy adults, with over 80% excreted unchanged in urine within 24 hours after a dose [12]. Elimination is mostly depended upon glomerular filtration and possibly some tubular excretion [12]. Short after introduction, vancomycin's clinical use was tempered due to (nephro)toxicity concerns. These could mainly be attributed to impurities present in these early formulations, which gave vancomycin its brownish colour and renowned nickname 'Mississippi mud' [10]. To date, the introduction of purified formulations, routine use of therapeutic drug monitoring to individualize dosages and increased use of continuous infusion dose regimens have minimalized vancomycin nephrotoxicity [13,14].

OPTIMAL DOSING OF ANTIBIOTICS

When designing dose regimens for antibiotics like aminoglycosides and vancomycin, it is crucial to consider exposure targets that maximize efficacy while minimizing toxicity. For efficacy, this target concentration relies heavily on the susceptibility of the offending pathogen. This susceptibility is expressed as the minimal inhibitory concentration (MIC), which is specific for each combination of a drug and pathogen. Three different general exposure-response relations or 'PK/PD indices' have been defined to link exposure metrics, MIC and efficacy: (1) the ratio of the maximum (unbound) drug concentration to the MIC (fC_{max}/MIC), (2) the ratio of the area-under-the-curve of the unbound drug to the MIC (fAUC/MIC) or (3) the percentage of time over a 24 hour period that the (unbound) drug concentration is above the MIC (%fT>MIC) [15,16]. PK/PD indices are determined by investigating multiple dosing strategies with varying dosing intervals in *in vitro* or *in vivo* animal research, thereby resolving which parameter (fAUC/MIC, fC_{max}/MIC or (%fT>MIC) correlates best with a parameter that reflects outcome (survival, pathogen load, etc). Based on these studies an antibiotic is allocated to one of these categories and used as a driver for dose adaptation strategies. Ideally, this knowledge is combined with a toxicity threshold, although toxicity is usually less well studied since most antibiotics are relatively well tolerated. In such toxicologic studies, drug concentrations (for example AUC or trough concentrations) are directly correlated to the risk of toxicity, as this is obviously independent of pathogen susceptibility. This approach to design dose regimens for antibiotics has nowadays become widely accepted, although there are some limitations [15]. For example, exposure metrics can be highly correlated, as is the case with AUC and C_{max}, with individuals with a high AUC often also having a high C_{max}, which complicates discrimination between these PK/PD indices. Also, the choice of PK/PD indices is sensitive to the study design, for example whether or not a continuous infusion regimen has been included [15]. Lastly, PK/PD indices show some dependency towards pharmacokinetic processes such as drug clearance [15].

For gentamicin, tobramycin and vancomycin, strong relationships between blood concentrations and efficacy/toxicity have been described. Regarding the aminoglycosides, mostly preclinical studies have shown that both C_{max}/MIC and the 24-hour AUC (AUC_{24h})/MIC are predictive for effectiveness, where in many situations these PK/PD indices are correlated [17–19]. Since the total 24-hour exposure can be difficult to measure in clinical practice, reaching a sufficient peak level has long been considered the primary target for aminoglycoside dosing. Currently, most evidence points to AUC_{24h}/MIC as parameter driving aminoglycoside efficacy [15,19–21]. The most convincing evidence comes from individuals with a reduced clearance, for example due to renal impairment, where the correlation between C_{max} and AUC_{24h} disappears [15]. Recently, AUC_{24h}/MIC as driver for aminoglycoside efficacy has also been adopted by leading susceptibly testing organisations such as USCAST and EUCAST [22,23]. For aminoglycosides, serum drug levels also strongly correlate to toxicity, where trough levels above 1 mg/L increase the risk on nephro- and ototoxicity [7]. For vancomycin, both efficacy and toxicity correlate with the AUC_{24h}. Several studies have shown that to maximize vancomycin's efficacy (at least for treating *S. Aureus* infections) the AUC_{24h}/MIC should be at least 400 (which corresponds to an AUC_{24h} of 400 mg*h/L for an MIC of 1 mg/L) [24–28]. Vancomycin related (nephro)toxicity appears to be more frequent in patients with AUC_{24h} exposures >700 mg*h/L [14]. Based on this data, the recently revised, leading vancomycin dosing guideline drafted under aegis of several American organisations of infectious diseases specialists and pharmacists recommends to target an AUC_{24h} of 400 – 700 mg*h/L [29].

OBESITY AND DRUG DISPOSITION

Over the last five decades, the global prevalence of overweight and obesity, defined by the World Health Organisation (WHO) as an 'abnormal or excessive fat accumulation that may impair health', has increased enormously [30,31]. In adults, obesity is typically quantified using the Body Mass Index (BMI, in kg/m^2), which is the ratio of the body weight (in kg) and the square of the height (in m). Cut-offs for BMI values in overweight and obesity are ≥25 kg/m^2 and ≥30 kg/m^2, respectively, while morbid obesity, also known as Class III obesity, is generally defined as a BMI ≥40 kg/m^2 [30]. In their guideline, Dutch bariatric surgeons defined a BMI ≥40 kg/m^2 or ≥35 kg/m^2 in the presence of obesity-related comorbidities such as diabetes mellitus or hypertension as one of the indications for bariatric surgery [32]. For children and adolescents, BMI is age and sex dependent. Therefore, typical growth charts are used to identify under- or overweight. Children in the 85th – 95th BMI-percentile, adjusted for gender and age, are considered overweight, whereas children above the 95th percentile are regarded as obese [33]. Another, related definition defines paediatric overweight and obesity as being more than 1 or 2 standard deviations, respectively, above the age and gender adjusted median of the growth reference line [34].

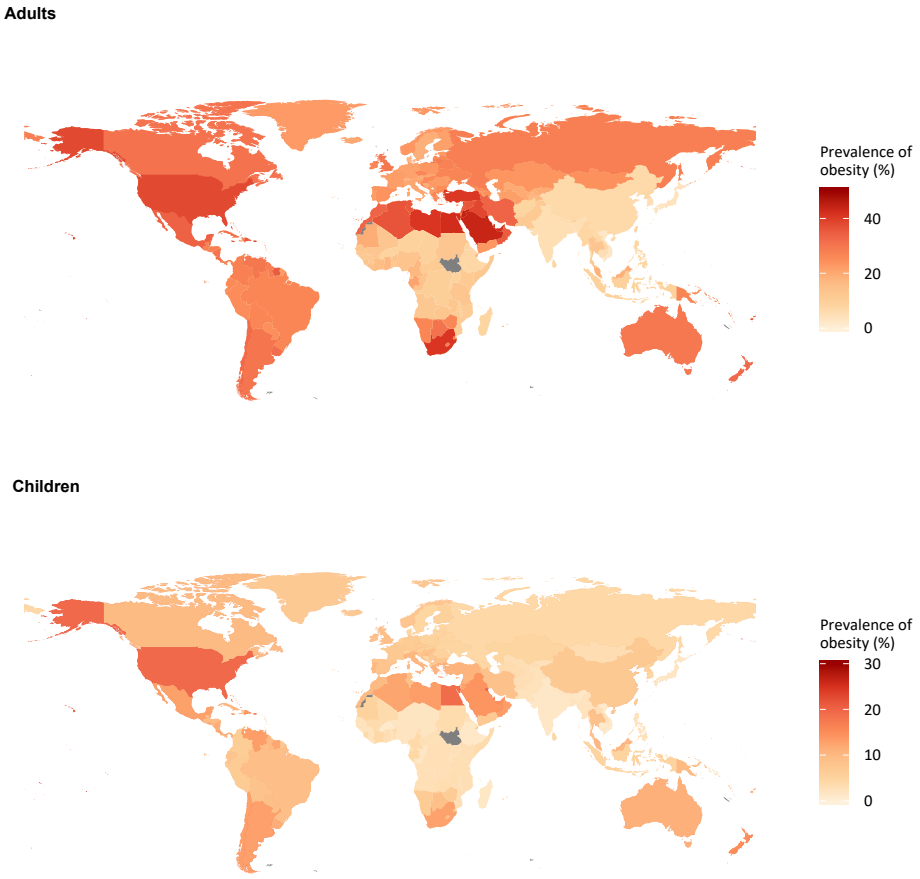

Figure 1. Worldwide prevalence of obesity for adults (upper panel, defined as BMI ≥30 kg/m²) and children (lower panel, defined as a BMI-for-age ≥2 standard deviations from median BMI-for-age). Data used from the NCD Risk Factor Collaboration (NCD-RisC) [31,34].

Since 1975, the global prevalence of adult obesity (BMI ≥30 kg/m²) tripled from 3.2% and 6.4% to 10.8% and 14.9% in men and women, respectively [31]. In regions such as Northern America, the Middle East and Northern Africa, over 30% of the adult population is nowadays considered obese (Figure 1). In some countries, the mean BMI increased with more than 1.5 kg/m² per decade since the 1970s. If these trends continue, global prevalence of obesity will reach 18 – 21% by 2025 [31]. Similar alarming trends are seen in children and adolescents (Figure 1) [34]. The past five decades global prevalence of childhood obesity increased from virtually non-existent (0.7% for girls and 0.9% for boys) to 5.6% and 7.8% for girls and boys, respectively [34]. In the United States of America, about one in every five infants shows excessive weight [34]. Obesity increases the risk on several diseases, such as hypertension, cardiovascular diseases, diabetes mellitus and certain types of cancer and is associated with an increased mortality

[30]. In 2015, around four million global deaths were attributed to a high BMI, mostly due to cardiovascular diseases [35]. Obesity also has a strong link with infectious diseases, as it appears to have a profound effect on the immune system, thereby increasing the susceptibility for infections [36]. Recently, this has been strikingly illustrated for COVID-19, where studies show that patients with a BMI > 35 kg/m^2 were two times more likely to be admitted to a critical care unit than normal weight patients [37].

The rapid escalation of obesity prevalence necessitates knowledge on how to dose drugs in obese patients. Obesity is associated with many (patho)physiological changes that may influence the pharmacokinetics of drugs [38]. The most striking impact is the increase in fat mass which can impact drug distribution into the body. Although the magnitude of this effect on drug distribution is often assumed to be related to a drug's lipophilic properties, there has been an increasing number of reports showing that lipophilicity alone is not a good predictor for changes in drug distribution [39]. Other, maybe less discernible but perhaps even more important physiological shifts occur with obesity. Due to an increase in cardiac output, blood flow to the kidney and liver, key organs in drug elimination, can be enhanced which can lead to in increased drug clearance. Here, we should however take into account that hepatic drug clearance is the result of liver flow, protein binding and intrinsic hepatic clearance, all of which can be differently impacted by obesity [40]. Regarding the intrinsic hepatic clearance, there is increasing evidence that overweight influences the activity of important drug metabolizing and transporting enzymes, where activity can be either decreased, increased or unaffected [40,41]. Due to pathological processes, such as non-alcoholic fatty liver disease (NAFLD) or a chronic increase in intraglomerular pressure, obesity ultimately might lead to a decline in liver- or renal function [42,43]. Taken together, it remains highly complex to predict the influence of obesity on a drug's clearance.

Estimating the renal function to guide drug dosing can be an additional challenge in obesity. In clinical practice, it is common to estimate a patient's renal function (depicted by the glomerular filtration rate or GFR) by using equations that incorporate serum creatinine (a breakdown product of creatinine phosphate in the muscle) and patient characteristics such as body weight, race or gender. Commonly used equations are the Modification or Diet in Renal Disease equation (MDRD), Chronic Kidney Disease Epidemiology equation (CKD-EPI), the Cockcroft-Gault equation (CG) or, in paediatrics, the Schwartz equation [44–46]. These equations have been developed in a predominantly non-obese population originally to be used to diagnose and stage kidney disease. MDRD, CKD-EPI and Schwartz estimate GFR are standardized to a body surface area of 1.73 m^2, which is also referred to as 'indexation'. CG uses total body weight (TBW) as a variable, where the estimate increases with body weight. As a result, these equations can possibly overpredict the absolute GFR (in mL/min) when used to estimate renal function in obese individuals. To correct for this overprediction, other body

size descriptors have been proposed to use as alternative for total body weight in the CG formula, where most studies advocate the use of lean body weight (LBW) [47–49]. Moreover, it remains a topic of debate how these equations perform in predicting clearance of renally excreted drugs in obesity [50].

DOSING GENTAMICIN, TOBRAMYCIN AND VANCOMYCIN IN OBESE PATIENTS

When treating severe infections with aminoglycosides or vancomycin, obtaining an optimal exposure is paramount to ensure a high efficacy with minimal risk of toxicity. Therefore, clinicians must consider the potential differences in pharmacokinetics related to obesity when using these antibiotics in obese patients.

In normal weight patients, gentamicin and tobramycin are usually dosed on the basis of body weight, typically 5 – 7 mg/kg [23]. Dosing of gentamicin and tobramycin in obesity has been subject to investigations since their first introduction [51–58]. Since these drugs are hydrophilic and, in the past, peak concentrations were assumed to be the primary driver of aminoglycoside efficacy, most of these studies have focused on characterizing changes in distribution volume. Unfortunately, only few report on clearance of aminoglycosides in obese individuals, even though to date drug clearance is the primary parameter of interest since this determines exposure and drives efficacy. In these studies, mostly conducted in individuals with a normal renal function, conflicting conclusions are reported, where some report that clearance correlates with body weight [52,54], while others found a relationship between aminoglycoside clearance and renal function estimates [55,56]. Moreover, a large part of these trials were conducted before the turn of the century, in a time where obesity was commonly defined as a total body weight above 20% of the 'ideal body weight'. As a consequence, 'obese' patients in these studies typically had a mean body weight around 85 – 100 kg, which today would at most be classified as moderately obese. Results from these studies therefore cannot simply be extrapolated to the obese individuals we nowadays see in clinical practice. Given the lack of high-quality evidence on this matter, we still remain ignorant as to if and how the gentamicin or tobramycin dose should be adapted in (morbidly) obese individuals with and without renal impairment.

The same applies to dosing vancomycin in overweight and obese adults. A widely accepted vancomycin therapeutic guideline published in 2009 by American infectious disease specialists and pharmacists, recommended a rather broad dose regimen of 15 – 20 mg/kg 2 – 3 times daily for both non-obese and obese patients [14]. This recommendation is based on several studies that were mostly performed with sparse data consisting of routinely collected peak

and trough levels [59–64]. Unfortunately, conclusions on how clearance changes with obesity differ between these studies. Similar to what is reported for aminoglycosides, some authors found body weight to be the most predictive covariate, while others describe clearance using renal function estimates or a combination of covariates. This might be explained by differences in study population with respect to renal function and body weight, or in study design. Considering the latter, accurate assessment of pharmacokinetic parameters and covariates has been shown to be highly sensitive to the sparseness of the data, for example when there is a low variability and range in time after dose or a low number of samples per individual [65]. This can be relevant when there is only TDM data consisting of peak and trough concentrations available for analysis as is the case for many of these studies. Altogether, there is currently no consensus on how vancomycin should be dosed in obese adults.

Even less evidence is available on vancomycin dosing in obese adolescents and children. In general, the basic principles discussed for obese adults presumably also apply to obese children and adolescents, although well-designed studies that explore this are limited [40,66]. Specifically for vancomycin, a small number of retrospective studies show that with similar mg/kg dosing, higher trough concentrations (as a marker for 24-hour exposure) are achieved in obese children compared to their non-obese counterparts, so a dose adjustment seems necessary [67–69]. Characterization of the pharmacokinetics in obese children can be particularly complex since processes of maturation, growth and increasing fat-mass intermingle. A weight-excess model that was recently proposed for midazolam pharmacokinetics in obese and non-obese adolescents, has not been investigated yet for vancomycin [70]. Several maturation functions for vancomycin clearance have been published, however both adolescents and obese individuals were underrepresented in these studies [71,72]. Given the fact that prevalence of obesity in this group increases alarmingly, the full pharmacokinetic profile of vancomycin in paediatric obesity need to be urgently characterized to design specific dosing guidelines for this group [66,73].

POPULATION PHARMACOKINETIC MODELLING AND SIMULATION

To be able to answer the questions raised in the previous sections it is important to conduct studies with a sound design and pharmacokinetic analysis. A major, well established methodologic strategy is to use population pharmacokinetic modelling and simulation techniques. These are widely considered leading tools for understanding and quantifying drug behaviour across different patient populations to design rational drug dose regimens [74]. Using this approach, a population pharmacokinetic model is developed that defines the relationship between a dose and a drug's blood or tissue concentration(s) over time. These models consist

of structural pharmacokinetic parameters (such as volume of distribution or clearance, described as algebraic equations) with different sources of random variability (usually inter-individual variability and residual variability). Patient characteristics or time independent covariate effects (for example body weight or a genotype) can be identified as predictors for pharmacokinetic parameters and subsequently included in the pharmacokinetic model. The population approach is also known as non-linear mixed effects modelling (NLME). NLME is a particularly suitable technique for the topic of this thesis, since it is powerful in separating and quantifying the influence of combinations of covariates on pharmacokinetic parameters, such as obesity and renal function or obesity and maturation processes in paediatrics. After a model is developed, simulations are performed incorporating the random and fixed effects (so called stochastic simulations) using different dose regimens in a large number of virtual subjects to find the optimal dose regimen. To date, population pharmacokinetic modelling and simulation has become broadly accepted by drug registration authorities as essential components in drug development programs, especially to inform dose regimens for special populations [75–77].

AIMS AND SCOPE OF THIS THESIS

In this thesis we aim to characterize the influence of obesity on the pharmacokinetics of gentamicin, tobramycin and vancomycin in (morbidly) obese adults, in conjunction with other possibly relevant patient characteristics such renal impairment or (critical) illness as occurring in the real-world. Additionally, we aim to investigate the influence of obesity, renal function and maturation on pharmacokinetics in a clinical population of lean and overweight children and adolescents with and without renal impairment and were treated with vancomycin. With this knowledge, we intent to gain more knowledge on changes of such renally cleared drugs in obesity and provide dose recommendations for (morbidly) obese children, adolescents and adults for the studied drugs. Using these dose recommendations, we aim to improve antibiotic treatment for (morbidly) obese patients by maximizing the antibiotic's efficacy and minimizing toxicity.

In **Chapter 2**, a comprehensive overview is provided on what is currently known regarding the physiological changes associated with obesity and their influence on pharmacokinetics and/or pharmacodynamics of drugs. In the next section, we specifically quantify the influence of obesity on the pharmacokinetics of gentamicin, tobramycin and vancomycin in non-obese and morbidly obese, but otherwise healthy individuals. To this end, several prospective, rich-sampling, clinical studies were conducted, for which the results are presented in **Chapter 3** for gentamicin, in **Chapter 4** for tobramycin and in **Chapter 5** for vancomycin. In the third section, we extend our studies to two real-world, clinical special populations. In **Chapter 6**, the pharmacokinetic model and dose recommendations for gentamicin are extended by

combining the prospectively collected data in non-obese and morbidly obese otherwise healthy individuals with real-world clinical TDM data from (morbidly) obese patients treated with gentamicin. In **Chapter 7** we study the pharmacokinetics in a large multicentre clinical cohort of children and adolescents treated with vancomycin. Finally, in **Chapter 8**, a general discussion is provided where we summarize the results, reflect on the clinical impact of our results and lessons learned from these studies, discuss on future perspectives and provide overall conclusions.

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