Infections in peritoneal dialysis patients: Incidence, determinants and the association with peritoneal transport
van Diepen, A.T.N.

Citation for published version (APA):
INFECTIONS IN PERITONEAL DIALYSIS PATIENTS
Incidence, determinants and the association with peritoneal transport
INFECTIONS IN PERITONEAL DIALYSIS PATIENTS

Incidence, determinants and the association with peritoneal transport

Anouk Tessa Natasha van Diepen
Infections in peritoneal dialysis patients:
Incidence, determinants and the association with peritoneal transport
PhD Thesis, University of Amsterdam, The Netherlands
Online: http://dare.uva.nl

© 2015 Anouk T.N. van Diepen, Amsterdam, the Netherlands.
All rights reserved. No parts of this thesis may be reproduced, stored in a retrieval system or transmitted in any form or by any means without permission of the author.

Cover design: STUDIO | 0404 - Bregje Jaspers
Lay-out: Nicole Nijhuis, Anouk van Diepen
Printed by: Gildeprint, Enschede, the Netherlands

The studies presented in this thesis have been prepared and conducted at the Department of Internal Medicine, Division of Nephrology, Academic Medical Center, University of Amsterdam, the Netherlands, the Department of Clinical Epidemiology of the Leiden University Medical Center, University of Leiden, the Netherlands and the Department of Internal Medicine, Division of Nephrology, University Health Network, University of Toronto, Toronto, Ontario, Canada. A Kolff scholarship for students from the Dutch kidney foundation (KSBS 10.0047), a short-term fellowship from the European Renal Association - European Dialysis and Transplant Association (STF-124), a grant from Baxter Healthcare Corporation (12CECPDEU1002) and Stichting Nephron financially supported the research published in this thesis.

The printing of this thesis was financially supported by the Dutch Kidney Foundation, Leiden University Medical Center, University of Amsterdam, Baxter Nederland B.V., Shire Nederland B.V., Fresenius Medical Care Nederland B.V.
INFECTIONS IN PERITONEAL DIALYSIS PATIENTS

Incidence, determinants and the association with peritoneal transport

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graag van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 20 februari 2015, te 12.00 uur

door

Anouk Tessa Natasha van Diepen

geboren te Amsterdam
Promotiecommissie

Promotores:  Prof. dr. R.T. Krediet
             Prof. dr. F.W. Dekker

Copromotores:  Dr. D.G. Struijk
                Dr. T. Hoekstra

Overige leden:  Prof. dr. R.J.M. ten Berge
                Prof. dr. J.J. Homan van der Heide
                Prof. dr. J.M. Prins
                Prof. dr. A.H. Zwinderman
                Dr. W.H. Boer
                Dr. C.J.A.M. Konings

Faculteit der Geneeskunde
# Table of contents

**Chapter 1**  General introduction and outline  

**Chapter 2**  The association between dialysis modality and the risk for dialysis technique and non-dialysis technique-related infections.  

**Chapter 3**  Protein-energy wasting is a risk factor for infections in both hemodialysis and peritoneal dialysis patients.  
*Submitted for publication.*  

**Chapter 4**  The association between exit site infection and subsequent peritonitis among peritoneal dialysis patients.  

**Chapter 5**  A qualitative systematic review of the literature supporting a causal relationship between exit site infection and subsequent peritonitis in patients with end-stage renal disease treated with peritoneal dialysis.  
*Perit Dial Int 2013; 33: 604-610.*  

**Chapter 6**  The association between glucose exposure and the risk of peritonitis in peritoneal dialysis patients.  
*Submitted for publication.*  

**Chapter 7**  The first peritonitis episode alters the natural course of peritoneal transport in peritoneal dialysis patients.  
*Perit Dial Int 2014, in press. [Epub ahead of print]*  

**Chapter 8**  The mutual relationship between peritonitis and peritoneal transport.  
*Perit Dial Int 2014, in press.*  

**Chapter 9**  Summary and general discussion  

**Chapter 10**  Dutch summary/Nederlandse samenvatting
Chapter 11  Appendices  165

Chapter 12  PhD Portfolio  174
              List of publications  179
              Acknowledgements/Dankwoord  180
              Curriculum vitae  185
# Chapter 1

**General introduction and outline**

1.1 End-stage renal disease and dialysis 10

1.2 History of peritoneal dialysis 10

1.3 Epidemiology 12

1.4 Infections in peritoneal dialysis 13

1.4.1 Peritonitis

1.5 Determinants of infections 15

1.5.1 Dialysis modality

1.5.2 Protein-energy wasting

1.5.3 Exit site infection

1.5.4 Glucose and glucose degradation products

1.6 Peritoneal transport 17

1.6.1 Functional assessment of the peritoneum

1.6.2 Solute transport

1.6.3 Fluid transport

1.7 Objectives and outline of the thesis 20

1.8 Study design and data collection 20
Chapter 1

This chapter includes a brief introduction to end-stage renal disease (ESRD) and dialysis, a description of the history and epidemiology of peritoneal dialysis (PD), followed by an introduction of the determinants under study and an explanation of the principles of peritoneal transport. Finally, the outline and rationale for the study design and data collection of this thesis will be provided.

1.1 End-stage renal disease and dialysis

ESRD is a severe condition that develops as a result of various kidney diseases, leading to a final common pathway with the development of fibrotic or sclerotic damage. In clinical practice, ESRD has been defined by a GFR below 15 ml/min/1.73\(^2\), also known as stage 5 chronic kidney disease (CKD). The prevalence of ESRD in the Netherlands is approximately 900 per million population.\(^2,3\) Due to the aging population ESRD has become a major public health problem.\(^4,5\)

When ESRD causes uremic symptoms and influences life expectancy and its quality, renal replacement therapy (RRT) is necessary to keep patients alive.\(^6\) Kidney transplantation is the most desirable type of RRT. However, still, a severe shortage of transplantable kidneys exists. In addition, not all patients have a suitable living donor or fulfil the criteria to be placed on the transplant waiting list. Therefore, in a large portion of patients, dialysis is the only available alternative for survival. Once dialysis is required, essentially, two options exist: hemodialysis (HD) and PD. HD involves extracorporeal diffusion of waste products from the blood across an artificial membrane. A vascular access has to be created to be able to flush the patients’ blood through the dialyzer and back into the patient. In PD, the patients’ natural “third kidney” is used: the peritoneal membrane or peritoneum. Dialysate is instilled in the peritoneal cavity via a surgically inserted catheter and drained after a pre-defined dwell time. During a PD dwell, waste products and fluid are exchanged across the peritoneum from the blood. A dialysis-scheme adjusted to the patients’ fluid status and homeostatic condition is drawn to optimize the use of PD. However, over the years, the connection between the peritoneal cavity and the outer world has been a major risk factor for infections that could potentially threaten or terminate the use this treatment modality in the patient.

1.2 History of peritoneal dialysis

The concept of PD goes back to 1744. Stephen Hales and Christopher Warrick attempted to treat a patient with recurrent ascites by first removing the excess abdominal fluid before
using a leather tube to infuse a solution consisting of 50% water and 50% wine into the abdomen. However, more important work was done in 1894 when Starling et al. observed the changes in the intraperitoneal fluid volume in the first hours after injection of a hypertonic, hypotonic or isotonic solution into the peritoneal cavity. Subsequently studies showed that the peritoneal membrane is permeable to substances other than water and that the exchange of these substances depends on the concentration gradient between fluid and blood. Ganter started to perform PD in larger uremic animals. In 1923, he became the first to carry out a PD session in a uremic patient. Although the treatment suppressed the symptoms temporarily, the patient died shortly after. Quite some time later, in 1959, Boen published his doctoral thesis in which he described the first series of patients with acute renal failure treated with PD. Shortly after, Boen was responsible for the development of intermittent PD via the multiple puncture technique and the implementation of the automatic cycling machines. However, it only worked when Tenkhoff developed the permanent catheter named after him. This permanent catheter was the only practical access device that made PD acceptable as long-term therapy for patients with renal failure. However, frequent peritonitis accompanied by protein wasting prevented its use as successful long term treatment. More than 10 years later, Popovich and Moncrief were the first to apply and describe Continuous Ambulatory PD (CAPD) in 1978. This was based on calculations, showing that the low efficiency of PD could be compensated for by applying it continuously in a very simple way. This method made it possible to remove fluids and dialyze the blood continuously, creating a steady homeostatic state. Paradoxically, at first, their abstract entitled “novel portable-wearable equilibrium peritoneal technique” was rejected by the American Society for Artificial Internal Organs. Their CAPD fundamentals are still used in everyday clinical practice.

Until 1978, PD solutions were only available in glass containers. Patients had to connect and disconnect tubes and bottles to the catheter with each exchange. Because of the high number of connections and disconnections an increased risk of peritoneal infection was present. Oreopoulos from Toronto started using PD fluids in plastic bags. Once the dialysis solution was introduced into the abdominal cavity, the plastic bag could be rolled up and remained connected to the patient’s body for the duration of the treatment. To remove the solution, the bag was unrolled, and gravity pulled the used dialysis solution into the bag. At the end of the procedure, the bag was removed from the catheter and a fresh bag attached. This new technology offered patients more comfort, relative freedom and reduced the rate of peritonitis. Over the years, the risk of contamination by “connectology” remained a major concern. Buoncristiani and colleagues made an important discovery when they developed the flush before fill system, now evolved into the widely used double bag system. The drainage of the dialysis fluid from the abdomen in the empty bag washed out any contamination at the time of the connection. This approach has been shown in randomized trials to drastically reduce the peritonitis rate.
The discussion around “biocompatibility” and the potential harmful composition of the dialysis solutions started in the 1980s. The first review that discussed the topic was written by Topley et al. only in 1994. The authors emphasized that the composition of the non-physiological low pH and high concentrations of glucose and lactate contribute to alterations of the peritoneal membrane. Furthermore, Wieslander et al. showed that the formation of glucose degradation products (GDPs) during the heat sterilization procedure might be partly responsible for the detrimental effects of the PD fluids. In the 1990s, the first reports were published about clinical experience with new and more “biocompatible” dialysis solutions. Nowadays, this new generation of “biocompatible” PD solutions is thought to result in clinically relevant benefit without additional harm.

In the 90s, the discovery of icodextrin as an osmotic agent for dialysis solutions has been an important step forward in PD. Icodextrin has been developed in Manchester out of an intravenous high-energy nutrient source that was used in the management of patients with renal failure: “Caloreen”, a glucose polymer. Icodextrin has the advantage that it is a high molecular weight osmotic agent, dissimilar to glucose, and that it provides sustained ultrafiltration particularly useful during the long dwell. Furthermore, the efficacy and safety have been proven in a large, long-term, randomized controlled study. Nowadays, icodextrin is used by more than 30,000 patients worldwide in more than 55 countries. In developed countries penetration probably exceeds 50%.

Although further efforts have been made to improve dialysis solutions to diminish their detrimental influence on peritoneal membrane viability, no new solutions have been implemented in routine clinical practice during the last decade.

1.3 Epidemiology

Globally, approximately 200,000 ESRD patients use PD, which is 11% of the total dialysis population. Of these PD patients, 41% is treated in developed countries. In these countries, the proportion of the dialysis population treated with PD ranges between 0.7% in Luxembourg to 79.8% in Hong Kong. Worldwide, in only four countries the majority of the dialysis patients use PD: Hong Kong, Guatemala, El Salvador and Mexico. Over the last decade, the number of PD patients per million population increased in both the developed and developing parts of the world, although the increase in the number of HD patients was larger, and thus the proportion of PD patients in the developed countries decreased with 5.3%. The latter can be explained by the interaction between economic influences, physician’s preference, dialysis capacity and patient characteristics.

Not every patient is eligible for PD. The only absolute contraindication to PD is the presence of extensive adhesions in the peritoneal cavity, making it inaccessible. Relative contraindications
General introduction and outline

include severe psychological and social problems, abdominal hernias, colostomy, ileostomy, ischemic and inflammatory bowel disease, progressive neurological diseases, bowel cancer, severe arthritis, chronic obstructive pulmonary disease, severe diverticular disease of the colon and hepatitis B. However, with efforts from a multidisciplinary medical staff these contraindications can be overcome in almost all situations. Approximately 65% of the incident dialysis patients are eligible for both PD and HD. Observational studies that compared survival between HD and PD patient have shown a survival benefit for PD during the early years on dialysis. The most recent analysis of the ERA-EDTA Registry showed that such beneficial effect of PD on survival was also present for a follow-up of five years. However, although extensive adjustment for confounders was performed in many of these studies, residual confounding by indication cannot be excluded as an explanation for this finding. A study from Canada performed in patients that started dialysis electively in the outpatient clinic only, found no survival difference.

1.4 Infections in peritoneal dialysis

Infections are an important cause of hospitalization and the leading non-cardiovascular cause of death in dialysis patients. In PD, nowadays, the incidence of infectious complications is approximately one infection per dialysis year. Previous observational studies investigated risk factors that may increase the risk of infections in PD patients. Risk factors that have been associated with the overall burden of infections include acquired uremic immunodeficiency, the presence of comorbid conditions such as diabetes mellitus and institutionalized treatment. The distinction between infections that are a consequence of the PD treatment technique, such as peritonitis, and infections that are not induced by the dialysis treatment is important when causes and consequences of infections are investigated.

1.4.1 Peritonitis

Peritonitis is a serious complication in patients on PD and may lead to technique failure or - although seldomly - even to death. Peritonitis has been hypothesized to be an important cause of peritoneal transport alterations by inflammatory damage. Although the acute effects of peritonitis are well known and reversible, much more uncertainty is present on its long-term effects. These appear to depend on the number of episodes, time on PD, severity, causative microorganism, treatment, and whether the study concerns the acute phase or long-term changes.

Globally, the incidence rate of peritonitis ranges between 0.06 and 1.66 per dialysis year. This wide variation can be explained by differences in practice patterns and potentially publication bias, as single-center reports dominate the literature.
Previous studies investigated determinants of the risk of peritonitis. Established demographic risk factors for peritonitis include older age, female sex, black ethnicity, and lower socioeconomic status. Clinical comorbid conditions associated with the risk of peritonitis include diabetes mellitus, coronary artery disease, chronic lung disease, persistent hypertension and poor residual renal function. Clinical risk factors for peritonitis that might be modifiable by medical interventions include the quality of PD training, obesity, smoking, depression, hypoalbuminemia, hypokalemia, absence of vitamin D supplementation, and nasal Staphylococcus aureus carrier status.

Basically, five routes of entrance exist via which the microorganism that causes peritonitis may enter the peritoneal cavity. The most common source of peritonitis is touch contamination at the time of exchange, after which the bacteria enter the peritoneal cavity via the luminal surface of the PD catheter. Second, catheter-related peritonitis episodes are a consequence of microorganisms that enter the peritoneal cavity along the outer surface of the PD catheter. Exit site and tunnel infection predispose patients to these infections. Third, enteric peritonitis might be a consequence of gastrointestinal perforation (e.g. after abdominal surgery) or transmural migration across the intestinal tract. Diverticulosis and acute treatment of obstipation appear to increase the risk of transmural migration of microorganisms. Haematogenous peritonitis subsequent to dental procedures is uncommon and -if required- preventable with prophylactic antibiotics. In rare cases, gynaecological procedures may lead to ascending microorganisms from uterine or vaginal sources in the peritoneal cavity and subsequent peritonitis.

A patient with peritonitis usually presents with cloudy effluent or abdominal pain or both. Globally, peritonitis is diagnosed, according to the criteria developed by Vas, when at least two of the following three findings are present: abdominal pain, cloudy effluent with ≥100 white blood cells/µL and ≥50% polymorphonuclear cells and/or positive microbiological culture of the dialysate. Especially for study purposes it is important to realise that both recurrent and repeat, but not relapsing peritonitis, should be counted as new episodes.

Over the years, a shift in the distribution of Gram-negative and Gram-positive microorganisms that cause peritonitis has been observed. The changes in the PD connection technique and the additional introduction of the application of an antibiotic cream at the catheter exit site, has especially reduced the rate of Gram-positive peritonitis whereas the rate of Gram-negative peritonitis remained rather stable. Attempts to standardize initial antibiotic regimens in the phase in which culture results are not yet available have been made by the International Society for Peritoneal Dialysis (ISPD) and updated ever since.
1.5 Determinants of infections

As described previously, several determinants of infectious complications generally, and in particular peritonitis, have been investigated. In the present thesis, dialysis modality and protein-energy wasting were studied as determinants of the overall incidence of infections. Furthermore, exit site infection and glucose exposure were investigated as potential determinants of peritonitis.

1.5.1 Dialysis modality

In countries with a minority of PD patients, PD patients present with different baseline characteristics at the start of RRT compared with those on HD. Generally, PD patients are younger and have less comorbidity. This can be explained by the fact that PD is a home-based treatment that requires the ability to independently perform the exchanges. In addition, almost all patients who need an acute start of dialysis are treated with HD. Subsequently, both HD and PD patients develop infections on dialysis. Whether dialysis modality itself is a risk factor for infectious complications or patient characteristics completely explain an observed infection incidence difference between the two modalities is unclear. Previous North-American studies compared HD and PD patients and the risk of infection-related hospitalizations and reported inconsistent results. Some found an increased risk in PD patients, whereas others showed a higher risk in HD patients. Some authors found no difference. Although infection-related hospitalization is a good measure of the severity of the infection, the risk for less severe infections could not be evaluated in these studies.

1.5.2 Protein-energy wasting

Protein-energy wasting (PEW) is a term introduced by the International Society of Renal Nutrition and Metabolism (ISRNM) based on the paper of Fouque et al. in 2008. PEW comprises a state of wasting of protein and energy stores during which body reserves gradually tire out. In the dialysis population, PEW thrives on the detrimental combination of an increased need for nutritional components and a decreased intake. The increased need for nutritional components is a consequence of CKD and its accompanying comorbid conditions. Also the catabolic effect of the dialysis treatment itself and the presence of a proinflammatory state facilitate the need for intensified nutrition. Reported prevalences of PEW at the start of dialysis depend strongly on the method of assessment and vary across different populations. The four SGA subscales facilitate a comprehensive assessment of 1) recent weight loss, 2) dietary intake and gastro-intestinal symptoms, 3) loss of subcutaneous fat mass and 4) loss of muscle mass. To define PEW, the 7-point SGA classification can be subdivided in: 1–3 indicating severe PEW, 4–5 moderate PEW and 6–7...
a normal nutritional status. Using the 7-point SGA classification, a previous study in the database of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), showed a dose-response relationship between the degree of PEW and mortality. Observational studies have linked PEW to increased morbidity, but unfortunately lack specific information about the association between PEW and infectious complications.

1.5.3 Exit site infection
The criteria for the presence of an exit site infection have been defined by the ISPD and require purulent drainage from the exit site with or without erythema. Exit site infections have been associated to subsequent peritonitis. Therefore, the implementation of preventative measures is an important aspect of the PD training program. In addition to routine cleansing of the exit site, multiple options for preventative exit site care exist and can be implemented in accordance with physicians' preferences and financial resources. Antibiotic ointment at the exit site can be applied daily or only in response to a positive culture. Similarly, intranasal antibiotics can be applied monthly in proven Staphylococcus aureus carriers or after a positive culture only.

A variety of microorganisms may cause an exit site infection, but common pathogens are Staphylococci and Pseudomonas. Empiric treatment with antibiotics may be systemic or nonsystemic, but should at least cover Staphylococcus aureus. If the patient has a history of Pseudomonas infections, the antibiotic should also cover this pathogen.

The implementation of the above described preventative and therapeutic protocols has led to a steep decrease in the incidence of exit site infections. Recent reports indicate that the incidence of exit site infections decreased to approximately 1 episode per 100 PD months. Therefore, it is unclear whether the association between exit site infection and peritonitis would still be present in a contemporary cohort.

1.5.4 Glucose and glucose degradation products
Glucose is the standard osmotic agent for PD. The concentration in dialysis solutions ranges between 70 to 198 mmol/L. The advantage of glucose is that it is cheap and easy to manufacture, not immunogenic, readily metabolized and, most importantly, facilitates high ultrafiltration rates. Unfortunately, glucose has a high absorption rate and therefore has been associated with both negative systemic and local effects. Systemically, the high uptake of glucose may induce hyperinsulinism, hyperglycaemia and metabolic syndrome. The local exposure to extremely high glucose concentrations has been shown to result in diabetiform changes in membrane morphology. Furthermore, glucose and its GDPs have a toxic effect on the mesothelial cell layer of the peritoneum. Glucose inhibits mesothelial cell proliferation, whereas GDPs are cytotoxic for the mesothelial cell. Besides their direct toxicity, GDPs promote the formation of advanced glycosylation end products.
(AGEs), which accumulate especially in the vascular wall of peritoneal vessels and induce fibrotic alterations, neoangiogenesis and inflammation. Nowadays, a two-chamber bag system is used to reduce the formation of GDPs during the heat sterilization procedure. Long-term exposure to glucose and its GDPs has been hypothesized to compromise peritoneal host defense. Many in vitro, ex vivo and animal studies have been performed to investigate this hypothesis. These experimental studies have shown a detrimental effect of glucose and GDPs on the function of monocytes, peritoneal macrophages and neutrophils. Unfortunately, the majority of these studies cannot be translated to the clinical situation due to a lack of follow-up, non-realistic exposure levels or the absence of renal failure. Although exposure to glucose and GDPs appears to be harmful in non-clinical experiments, clinical studies demonstrated no effect on the susceptibility to peritoneal infection.

1.6 Peritoneal transport

The basis of peritoneal dialysis is the removal of excess water and solutes from the circulation under the influence of an osmotic gradient, provided by the dialysis solution. The process induced by this osmotic gradient is called peritoneal transport. The peritoneum plays a central role in peritoneal transport. It functions as a barrier membrane that determines the peritoneal permeability to water and solutes. Therefore, the monitoring of its function is of clinically relevant importance. In 1988 Krediet et al. argued that peritoneal transport of low molecular weight solutes is dependent on the effective peritoneal surface area (the number of pores), whereas that of macromolecules is also influenced by the intrinsic permeability of the membrane (the pore size). Around the same time Rippe et al. developed the so-called “three pore model” to describe the kinetics of peritoneal transport of small solutes, macromolecules and fluid through small pores (40 Å), large pores (> 150 Å) and ultrasmall intra-cellular pores(<5 Å), later identified as the water channel aquaporin-1. The model accurately predicts the transport of water, small solutes and macromolecules across the peritoneal membrane. The three pore model supports the interpretation of functional tests that assess the peritoneal membrane and helps to understand the (patho)physiologic aspects of peritoneal transport.

1.6.1 Functional assessment of the peritoneum

The efficacy of PD can be monitored by assessment of the peritoneal membrane function by peritoneal function tests. The first peritoneal function test was developed and introduced in clinical practice by Twardowski and colleagues. This so-called peritoneal equilibrium test (PET) consisted of a standardized four-hour dwell with 2 liters of 2.5%/2.27% glucose
PD solution. The test was relatively simple and allowed for reproducible calculations of transport rates of urea, creatinine, glucose, protein, potassium, and sodium.

Subsequently, a number of modifications of the PET have been developed. The modified PET as advocated in 2000 by the International Society for Peritoneal Dialysis is done with the most hypertonic dialysis solution and includes a plasma and dialysate Na\(^+\) determination for qualitative assessment of free water transport. Interesting advances thereafter include the one-hour mini-PET\(^{188}\) by La Milia et al., the four-hour modified PET with temporary drainage and re-instillation after one hour\(^{189}\) by Cnossen et al. which was further studied and renamed the two-in-one protocol\(^{190}\) by Bernardo et al. The mini-PET has the advantage that it only takes one hour and allows quantitative assessment of free water transport. However small solute transport is not comparable with values obtained after a 4 hours dwell, also not after correction for the dwell-time. The two-in-one modified PET includes an additional drainage after one hour followed by reinfusion. This allows for calculation of free water transport and provides more accurate estimates of solute transport after 4 hours. The two-in-one modified PET confirmed previous findings and further emphasized that this test provides reliable and useful clinical information concerning both small solute and fluid transport.

The Academic Medical Center – University of Amsterdam is the only center in the world that carries out the standardized peritoneal permeability analysis (SPA).\(^{191-193}\) Implementation of the SPA in other, non-academic nephrology departments is not feasible, because some determinations are very complicated. Initially, the SPA was developed for research purposes and later it was incorporated in routine clinical practice in the AMC. The SPA consists of a four-hour dwell with 3.86% glucose during which intermediate dialysis samples are collected at multiple pre-defined time points: 0, 10, 30, 60, 120, 180 and 240 minutes. In addition, blood samples are drawn twice (0 and 240 minutes). The major advantage of the SPA is that it involves a volume marker (dextran 70), which allows for estimation of the transcapillary ultrafiltration, effective lymphatic absorption, intraperitoneal volume, and residual volume. In addition, protein clearances can be calculated using the collected dialysate and blood samples.

A recent review further summarizes the pros and cons of the peritoneal function tests that have been developed over the years.\(^{194}\)

1.6.2 Solute transport

The small pore system is responsible for the transport of low molecular weight solutes. Small solute transport is mainly diffusive,\(^{195}\) which means that its transport is based on the difference between the solute concentration in the blood and the solute concentration in the dialysis solution. The effective peritoneal vascular surface area (the number of small pores) is the major determinant of small solute transport. In patients on long-term PD, some increase is present in the effective vascular surface area of the peritoneum.\(^{196}\)
Macromolecular solute transport occurs through the large pores (>250A) by both convective forces\textsuperscript{197,198} and restricted diffusion.\textsuperscript{199} This makes it likely that clearance of serum proteins is mainly dependent on the intrinsic permeability (average pore size). The intrinsic permeability of the peritoneal membrane to the transport of macromolecules can be expressed by the restriction coefficient, which is the slope of the relationship that is present between peritoneal clearances and the free diffusion coefficients of these proteins, when plotted on a double logarithmic scale.\textsuperscript{195,200} The radii of the large pores tend to become more restrictive with time on PD and consequently hamper transport of macromolecules in long-term PD.\textsuperscript{202,203}

1.6.3 Fluid transport

Fluid transport is determined by transcapillary ultrafiltration and lymphatic absorption. As described in section 1.4.4, transcapillary ultrafiltration involves an osmotic agent in the dialysis solution, which favors fluid transport from the circulation through pores in the capillary wall to the peritoneal cavity. In addition, ultra small transcellular pores exist, called aquaporin-1, which allow transport of water, but not of solutes.\textsuperscript{198,203} The functional tests that can be used to determine this so-called “free water transport” are described in section 1.5.1. The total volume of ultrafiltration is dependent on the osmotic gradient and the osmotic conductance to glucose. The osmotic gradient is dependent on the absorption of glucose, which is determined by the effective vascular surface area of the peritoneum.\textsuperscript{204} The osmotic conductance is dependent on the ultrafiltration coefficient and also on the resistance the peritoneal membrane exerts to glucose as osmotic agent (reflection coefficient). The latter is dependent on the number and function of water channels. Studies in peritonitis-free long-term PD patients have shown an initial increase in ultrafiltration during the first months on PD, which was followed by a gradual decrease during the time course of PD.\textsuperscript{196,205-208} In long-term PD, decreased free water transport due to impairment of the osmotic conductance is the main phenomenon that causes ultrafiltration failure.\textsuperscript{209,210} In addition, an increased effective vascular surface area may facilitate ultrafiltration failure through the rapid loss of an osmotic gradient.

Lymphatic absorption can be estimated with indirect methods only. The disappearance rate of intraperitoneally administered macromolecules from the peritoneal cavity or the rate of their appearance in the circulation can be used.\textsuperscript{211,212} Based on previous studies,\textsuperscript{213-215} it seems likely that lymphatic reabsorption from the peritoneal cavity remains stable over time on PD. However, a high lymphatic reabsorption rate can cause ultrafiltration failure early in the course of PD.\textsuperscript{210}
1.7 Objectives and outline of the thesis

The aim of this thesis was to investigate the incidence and determinants of infectious complications in PD patients, with the emphasis on peritonitis. Furthermore, the association between peritonitis and peritoneal transport was evaluated. In this first chapter, a general introduction has been given about the history and epidemiology of PD, followed by an introduction to the determinants under study and the principles of peritoneal transport. Finally, the outline and rationale for the study design and data collection of this thesis is provided.

In Chapter 2, the association between dialysis modality and the epidemiology of infectious complications is described. Infections were stratified in those that are related to the dialysis technique and those that are not technique-related, to distinguish effects of the technical aspects of the modality from immunological influences. The aim of Chapter 3 was to investigate the association between protein-energy wasting, defined by an SGA classification of 1-5, with the incidence rate of infections. Patients were assessed in strata of dialysis modality, because of the distinct epidemiology of infections in HD and PD patients. Traditionally, exit site infection has been thought to predispose PD patients to peritonitis, although the risks have not been quantified. Chapter 4 addresses exit site infection as a risk factor for subsequent peritonitis, whereas in Chapter 5 a qualitative review of the literature supporting the association between exit site infection and subsequent peritonitis is presented. Glucose is thought to impair the peritoneal host defense and may therefore lead to an increased risk of peritonitis. Chapter 6 evaluates the association between exposure to glucose during the first year of PD and the subsequent risk of peritonitis. In Chapter 7, the influence of the first peritonitis episode on peritoneal transport parameters is addressed. Subsequently, the focus of Chapter 8 is the impact of multiple peritonitis episodes on peritoneal function in patients that survived 3 years on PD.

1.8 Study design and data collection

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) was the main study population for the research conducted in chapter 2 and chapter 3. NECOSAD is a prospective and longitudinal Dutch multicenter cohort that included 38 dialysis centers and included over 2000 dialysis patients. Incident ESRD patients, aged ≥18 years, starting dialysis between 1 January 1997 and 1 January 2007 were eligible for inclusion. For the present NECOSAD sub-studies, we conducted a review of both in- and outpatient medical records of all patients from five dialysis centers that participated in NECOSAD: two tertiary care
university hospitals and the regional hospitals. The dialysis centers were chosen for pure practical reasons (travel distance and the number of included patients) to assure efficient data collection. No additional exclusion criteria were applied, despite the evident need for the medical records to be complete.

Patients included in a randomized controlled trial comparing mupirocin with Polysporin Triple for the prevention of catheter-related infection in PD patients (The MP³ study) were used as the study population for the research conducted in chapter 4. The initial primary end point of the trial was the time to first PD-related infection. This was a composite end point that included one or more of the following: exit site infection, tunnel infection, or PD peritonitis, as defined by ISPD guidelines. Secondary end points included the removal of the catheter for refractory infection, hospitalization due to PD-related infection, death due to PD-related infection, all-cause mortality, and transfer to HD. Before the start of the trial, patients were taught to apply the study ointment to the exit site with each dressing change. Patients were reminded to contact their dialysis team if either exit site infection or peritonitis was suspected. As part of the trial protocol, rigorous methods were used to record all exit site infections and peritonitis episodes prospectively. Ongoing direct patient contact and review of all dialysis unit logs and charts as well as formal study incident reports were carried out to assure good-quality data collection. All aspects of medical care, including exit site care, dressing change frequency, dialysis protocols, and management of PD-related infections, were left to discretion of the patient’s primary nephrologist. Trial results showed no significant decrease in PD-related infections with the routine use of Polysporin Triple at the exit site. The data safety monitoring board recommended continued follow-up even after the first PD-related infection for subsequent safety data analysis. As such, follow-up was continued in all patients until death, transfer to another unit, transplantation, or the end of the 18-month follow-up period, which facilitated the data for our study concerning the association between exit site infection and subsequent peritonitis.

The PD patients from the Academic Medical Center (AMC) – University of Amsterdam were used as the main cohort for the studies described in chapter 6, chapter 7 and chapter 8. In chapter 6 the association between glucose exposure and the incidence of peritonitis was assessed. Medical records were searched to retrospectively retrace the rinsing schemes during a patient’s first year on PD. From these schemes the exposure to glucose could be calculated. A novel and more advanced method, compared with those reported previously, was developed to be able to estimate the glucose exposure more precisely. Another advantage of the method is that it can be applied to both CAPD and APD patients. Furthermore, all peritonitis episodes of incident PD patients treated in the AMC were recorded in a large database.
The focus of chapter 7 is on the association between the first peritonitis episode and peritoneal transport parameters. Between 1990-2010, yearly SPA tests were performed routinely in all PD patients treated in the AMC. To address the question under study, patients with a first peritonitis episode and a SPA within the year before and after peritonitis are identified. Peritonitis-free patients with sufficient SPA data function as representatives of the natural course. In Chapter 8, two extremes were compared with assess the influence of multiple peritonitis episodes on peritoneal transport. Peritoneal transport parameters of peritonitis-free patients who survived the first 3 years on PD were compared with patients who survived both 3 years on PD and ≥ 3 episodes of peritonitis.
References


91. Lim WH, Johnson DW, McDonald SP. Higher rate and earlier outcomes of *Enterobacteriaceae* peritonitis in CAPD patients compared with non-Aboriginal patients with end-stage renal failure maintained on peritoneal dialysis in Australia: analysis of ANZDATA. *Nephrology (Carlton)* 2005; 10: 192-197.


Chapter 2

The association between dialysis modality and the risk for dialysis technique and non-dialysis technique-related infections

Anouk T.N. van Diepen, Tiny Hoekstra, Joris I. Rotmans, Mark G.J. de Boer, Saskia Le Cessie, Marit M. Suttorp, Dirk G. Struijk, Els W. Boeschoten, Raymond T. Krediet, Friedo W. Dekker

Nephrology Dialysis Transplantation 2014
Volume 29, pages 2244-2250

Comment in: Collier S and Davenport A. Reducing the risk of infection in end-stage kidney failure patients treated with dialysis. Nephrol Dial Transplant 2014; 29: 2158-2161
Abstract

Background: Infections are a major cause of morbidity and mortality among dialysis patients. Dialysis modality has been hypothesized to be a potential immunomodulatory factor. The objective of this study was to determine the influence of the first dialysis modality on the risk for infections on dialysis.

Methods: Our study was conducted utilizing The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) cohort of incident dialysis patients. Medical records of all patients from two tertiary care university hospitals and three regional hospitals were reviewed using pre-specified criteria. Information about infections was collected from the start of dialysis until death, modality switch, study withdrawal, kidney transplantation or at the end of the study. Age-standardized incidence rates for infections were calculated. Poisson regression analysis was used to calculate adjusted incidence rate ratios (IRR).

Results: In total, 452 patients, of whom 285 started with hemodialysis (HD) and 167 with peritoneal dialysis (PD) were included. The median follow-up time on the first dialysis modality was similar for HD and PD, 1.8 and 2.0 dialysis years, respectively. During the first 6 months, the age-standardized infection incidence rate was higher on HD compared with PD patients ($p=0.02$). Overall, PD patients had a higher infection risk (adjusted IRR: 1.65, 95% confidence interval (CI): 1.34-2.03), which could be attributed to a fourfold increased risk for dialysis technique-related infections. The risk for non-dialysis technique-related infections was lower in PD patients (adjusted IRR: 0.56, 95% CI: 0.40-0.79).

Conclusions: Overall, PD patients carry a higher risk for infections. Interestingly, the risk for non-dialysis technique-related infections was higher in HD patients. The links between dialysis modality and the immune system is expected to explain this difference, but future studies are needed to test these assumptions.
Introduction

Infectious complications among both hemodialysis (HD) and peritoneal dialysis (PD) patients are a major cause of morbidity, hospitalization\textsuperscript{1-7} and the leading non-cardiovascular cause of death.\textsuperscript{8} A few studies compared HD and PD and the risk for infection-related hospitalization and reported contradicting results.\textsuperscript{2-5,7} In these studies, the incidence of infection-related hospitalizations among HD patients ranged between 0.29-1.39 per dialysis year, whereas in PD patients, incidence rates between 0.42-1.38 per dialysis year were observed. In some studies, an elevated infection risk in PD patients was observed,\textsuperscript{2,7} which could predominantly be explained by peritonitis, whereas others revealed a higher risk for infection in HD patients.\textsuperscript{3} However, the majority of studies\textsuperscript{3-5,7} only reported infections leading to hospitalization and did not evaluate whether dialysis modality altered the risk for less severe infections. Thus, an association between dialysis modality and the risk for overall infectious complications has not been well established. Furthermore, it has not been made evident whether the incidence rate of infections is constant over time, highest directly after the start of renal replacement therapy or increases with time on dialysis.

As expected, dialysis technique-related infections, like peritonitis and vascular access-associated sepsis, were found to be modality-associated.\textsuperscript{2,4,5,7} Remarkably, these studies also showed a higher incidence rate of pneumonia in HD patients. A likely explanation is that HD patients are often older and suffer from more comorbidity than PD patients. However an increased risk for pneumonia remained present after adjustment for these confounding factors.\textsuperscript{7} Alternative explanations may be that initiation of HD, compared with PD, is associated with distinct immunological alterations or different environmental exposure.\textsuperscript{9-14} These factors may lead to an altered risk profile for non-dialysis technique-related infections.

The aim of the present study was to elucidate the association between dialysis modality and infectious complications. The study was designed to investigate the influence of the first dialysis modality on the risk for overall infectious complications, dialysis technique- and non-dialysis technique-related infections. In addition, the risk for infectious complications over time on the first dialysis modality was compared. We hypothesized that PD patients develop more infections on dialysis, whereas HD patients carry a higher risk for infection directly after the start of dialysis.

Materials and methods

Study design
The present study was conducted in The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study cohort. NECOSAD is a multicenter prospective cohort study...
of dialysis patients from 38 centers in the Netherlands. Incident end-stage renal disease patients, aged ≥18 years, starting dialysis between 1 January 1997 and 1 January 2007 were eligible for inclusion. Medical ethics committees of all participating hospitals approved the study. All participants gave their written informed consent. For the present study, we conducted a review of both in- and outpatient medical records of all patients from five dialysis centers who participated in NECOSAD: two tertiary care university hospitals and three regional hospitals. No exclusion criteria were applied. The dialysis centers were chosen for practical reasons (travel distance and the number of included patients) to assure efficient data collection. Patients were censored at modality switch, withdrawal from the study, transfer to a non-participating dialysis center, kidney transplantation, death or at the end of the study follow-up period in June 2009.

Data collection
Data on infectious complications were retrospectively collected using strictly pre-specified criteria (described below). Information about the incidence and microbiology of infections was collected from the start of renal replacement therapy until death or censoring. Data collection was conducted by two reviewers (A.T.N.v.D. and M.M.S.). To ensure good-quality data collection, the reviewers applied strictly pre-specified criteria, which were developed to minimise the risk of reviewer bias. The reviewers worked in close collaboration during the full reviewing process. Discrepancies were resolved by a third party (R.T.K.). Demographic data collected included dialysis modality, age, sex, diabetes and other co-morbidities, ethnicity, educational level, smoking, dialysis preparation in an outpatient setting, primary kidney disease grouped into four categories, body mass index (BMI), Kahn comorbidity score, medication, C-reactive protein (CRP), haemoglobin and serum albumin. The Kahn comorbidity score is calculated based on a combination of age and the number of comorbid conditions. Patients are classified into low, medium and severe mortality risk. The Kahn comorbidity score has been validated in NECOSAD cohort and was found to perform equally appropriate when compared with Davis and Charlson comorbidity indices.

Infection definitions
In general, infection is defined as a host response to invading microorganisms. The presence of microorganisms without a host response is no evidence of infection. In contrast, an inflammatory response is not necessarily a presentation of infectious invasion, but may also result from other proinflammatory stimuli. Therefore, scoring criteria for infections were strictly pre-specified to secure good-quality data collection. An infection was considered present when (i) diagnosed by a nephrologist or other physician and (ii) supported by evidence such as a positive culture, radiologic confirmation, or antibiotic, antiviral, or antifungal treatment. The diagnosis was required to be accompanied by treatment in case of
a soft tissue infection, a respiratory tract infection other than pneumonia and urinary tract infections. All infections were categorized as shown in Table 1. Infections were classified as dialysis technique-related infection and non-dialysis technique-related infections. The International Society for Peritoneal Dialysis guidelines/recommendations were used to define recurrent, relapsing, and repeating infectious episodes. Both recurrent and repeating, but not relapsing, infectious episodes were scored as a new infection.

Table 1. Categorization of infectious complications

<table>
<thead>
<tr>
<th>Dialysis technique-related infection</th>
<th>Non-dialysis technique-related infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access infections</td>
<td>Cardiac infections</td>
</tr>
<tr>
<td>Vascular access associated sepsis</td>
<td>Gastrointestinal infections</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>Respiratory infection</td>
</tr>
<tr>
<td></td>
<td>Non-vascular access associated sepsis</td>
</tr>
<tr>
<td></td>
<td>Soft tissue infections</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
</tr>
</tbody>
</table>

Statistical analyses

Differences in baseline characteristics were tested with an unpaired Student’s t-test, Mann-Whitney (continuous data) or chi-square test (categorical data). Incidence rates are expressed as infections per dialysis year. To adjust for age differences between PD and HD patients, weights derived from the age distribution of the complete study population were used for direct standardization. Age-standardized infection incidence rates were calculated in time intervals after the start of dialysis. Adjusted Poisson regression models with robust standard errors were used to assess the association between the first dialysis modality and the risk for overall infections and specific types of infections. Crude and adjusted incidence rate ratios (IRRs) were calculated to estimate both the overall infection risk and the risk for infectious complications over time. Adjustments were made for baseline measurements of age, sex, diabetes, ethnicity, BMI, primary kidney disease, Kahn comorbidity score, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting. To assess the influence of HD vascular access on the incidence rate of dialysis technique-related infections among HD patients, we used data collected by previous chart review and calculated the adjusted IRR for dialysis technique-related infections in patients with an arteriovenous graft or fistula at 3 months compared with those with a central venous catheter. A likelihood ratio test was performed to determine whether the effect of dialysis modality on the risk for infectious complications changed with the time spent on dialysis. The statistical analyses were performed using Statistical Package for the Social Sciences (IBM SPSS Statistics 20) and STATA (Stata/IC 12.1).
Results

Population characteristics

Medical records of 471 NECOSAD patients were reviewed. After excluding patients with incomplete or lost files (n=19), a total of 452 patients could be included. The baseline characteristics of the study population are summarized in Table 2. In total, 285 (63%) started with HD and 167 (37%) with PD as their first modality of renal replacement therapy. At the start of dialysis, patients on HD were older, more often Caucasian, had a higher Kahn comorbidity score and a lower haemoglobin level compared with PD patients. The median follow-up time on the first dialysis modality was 1.8 years (interquartile range (IQR): 0.6-3.7) on HD and 2.0 years (IQR: 0.8-3.5) on PD (p=0.76), with a maximum of 11.3 years. During follow-up, 35 (12%) HD patients were censored due to a switch to PD, whereas 58 (35%) PD patients were censored due to a switch to HD. Less than 2% of the data on confounding factors were missing. When compared with the complete NECOSAD study cohort, the patients included in this study had similar baseline characteristics (data not shown).

Table 2: Baseline characteristics of the study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD</th>
<th>PD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>285</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>Age start dialysis (median;range)</td>
<td>69.0 (19-88)</td>
<td>54.6 (19-80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (%)</td>
<td>66</td>
<td>63</td>
<td>0.51</td>
</tr>
<tr>
<td>BMI kg/m² (mean (SD))</td>
<td>25.5 (4.2)</td>
<td>25.2 (3.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Ethnicity (%Caucasian)</td>
<td>95</td>
<td>83</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>23</td>
<td>17</td>
<td>0.13</td>
</tr>
<tr>
<td>Cause of ESRD (%)</td>
<td></td>
<td></td>
<td>0.29</td>
</tr>
<tr>
<td>Renovascular disease</td>
<td>24</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>16</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>47</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>Kahn comorbidity score (% category 3)</td>
<td>36</td>
<td>21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Present</td>
<td>21</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>49</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>30</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>CRP* (mg/L) (median;IQR)</td>
<td>6 (3-16)</td>
<td>4 (3-9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin* (g/dl) (mean (SD))</td>
<td>10.9 (1.4)</td>
<td>11.7 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum albumin* (g/dl) (mean (SD))</td>
<td>3.21 (0.8)</td>
<td>3.25 (0.8)</td>
<td>0.78</td>
</tr>
<tr>
<td>HD vascular access (% CVC)*</td>
<td>11</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Dialysis preparation in an outpatient setting (%)</td>
<td>68</td>
<td>92</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, Body mass index; ESRD, End-stage renal disease; CRP, c-reactive protein; CVC, central venous catheter; N/A, not applicable; SD, standard deviation; IQR, interquartile range.* levels or % after 3 months on dialysis.
Association between dialysis modality and infections

Infection incidence rates

During follow-up, patients on HD experienced 448 infections (0.65/patient/dialysis year) and patients on PD suffered from 355 infections (0.91/patient/dialysis year) on the first dialysis modality. Infection incidence rates over time, standardized for age and stratified by dialysis modality are shown in Figure 1. Within the first 6 months after the start of dialysis, HD patients had a significantly higher age-standardized incidence rate of infectious complications compared with PD patients: 1.72 infections/dialysis year (95% Confidence interval (CI): 1.62-1.81) compared with 1.40 infections/dialysis year (95% CI: 1.21-1.58) \( (p=0.02) \). After 6 months, the age-standardized incidence rate of infections was higher in PD patients compared with HD patients. During the complete follow-up period, the incidence rate of non-dialysis technique-related infections was higher in HD patients, whereas that of dialysis technique-related infections was higher in PD patients.

Association between dialysis modality and overall infectious complications

Crude and adjusted IRRs are presented in Table 3. The risk for infectious complications was significantly higher in PD patients compared with HD patients, with an adjusted IRR of 1.65. This higher risk can be attributed to the increased risk for PD patients to develop dialysis technique-related infections, like peritonitis and access infection, with an adjusted IRR of 4.10. However, HD patients with a fistula at 3 months had a lower risk for dialysis technique related infections (adjusted IRR: 0.28; 95% CI: 0.14-0.55) compared with those with a catheter, whereas an arteriovenous graft resulted in a similar infection risk (adjusted IRR: 0.96; 95% CI: 0.45-2.05). The overall risk for non-dialysis technique-related infection was lower in PD patients compared with HD patients with an adjusted IRR of 0.56. The latter could be explained by a higher risk for non-vascular access-associated sepsis (adjusted IRR: 0.24) and respiratory infections (adjusted IRR: 0.58) in HD patients.

Figure 1. age-standardized dialysis technique- and non-dialysis technique-related infection incidences per dialysis year over time. More detailed information about specific types of infections over time can be found in an online supplemental figure (see appendix 1 in chapter 10 of this thesis)
Table 3. Incidence rates and (adjusted) Incidence rate ratios of infectious complicationsα

<table>
<thead>
<tr>
<th></th>
<th>Incidence rates per 1000 dialysis year</th>
<th>Crude IRR</th>
<th>Adjusted IRR*</th>
<th>Adjusted IRR**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total infection</td>
<td>653</td>
<td>914</td>
<td>1.29 (1.08-1.53)</td>
<td>1.31 (1.09-1.57)</td>
</tr>
<tr>
<td>Dialysis technique-related infection</td>
<td>212</td>
<td>731</td>
<td>3.25 (2.57-4.11)</td>
<td>2.94 (2.28-3.78)</td>
</tr>
<tr>
<td>Access infection</td>
<td>137</td>
<td>368</td>
<td>2.55 (1.95-3.35)</td>
<td>2.05 (1.54-2.73)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>19</td>
<td>358</td>
<td>21.29 (11.17-40.58)</td>
<td>22.57 (11.38-44.78)</td>
</tr>
<tr>
<td>Vascular access associated sepsis</td>
<td>56</td>
<td>5</td>
<td>0.09 (0.02-0.36)</td>
<td>0.09 (0.02-0.40)</td>
</tr>
<tr>
<td>Non-dialysis technique-related infection</td>
<td>441</td>
<td>183</td>
<td>0.40 (0.29-0.53)</td>
<td>0.47 (0.34-0.64)</td>
</tr>
<tr>
<td>Non-vascular access associated sepsis</td>
<td>118</td>
<td>21</td>
<td>0.17 (0.08-0.36)</td>
<td>0.17 (0.08-0.35)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>16</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Gastro-intestinal</td>
<td>38</td>
<td>41</td>
<td>1.09 (0.57-2.08)</td>
<td>1.13 (0.54-2.34)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>152</td>
<td>54</td>
<td>0.34 (0.20-0.57)</td>
<td>0.47 (0.25-0.80)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>21</td>
<td>5</td>
<td>0.12 (0.02-0.92)</td>
<td>0.13 (0.01-1.29)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>96</td>
<td>62</td>
<td>0.60 (0.36-1.00)</td>
<td>0.71 (0.42-1.19)</td>
</tr>
</tbody>
</table>

αHD is the reference category. * Incidence rate ratio adjusted for age, sex and diabetes; ** + BMI, Kahn co-morbidity score, Primary kidney disease, ethnicity, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting. N/A: Incidence rate ratio not available.
Association between dialysis modality and infection risk over time

The adjusted IRRs over time are reported in Table 4. Directly after the start of dialysis, the overall infection risk was somewhat lower in PD patients with an adjusted IRR of 0.87, although not significant. The incidence rate of infections in HD patients decreased substantially after 3 months, whereas the incidence rate in PD patients remained stable (Figure 1). Therefore, after 6 months, the adjusted IRRs were significantly higher for PD patients and differences became larger over time. For the interaction between time on dialysis and dialysis modality the complete follow-up time on the first dialysis modality was taken into account. The time after the start of dialysis, divided into intervals of 6 months, modified the association between the first dialysis modality and the risk for infections (likelihood-ratio test, \( p < 0.001 \)).

Sensitivity analyses

Similar results were observed when patients followed <90 days after the start of dialysis (n=50) were excluded from the analysis, which emphasizes that our sample of the NECOSAD cohort included stable incident dialysis patients. Of all patients, 38 died before experiencing an infection. Of these, 32 were treated with HD and 6 with PD. When the adjusted subhazard ratio with death as a competing risk was calculated, the adjusted IRR was somewhat attenuated for overall infection (1.42; 95% CI: 1.08-1.88). Of all infections, 338 (75%) on HD and 179 (50%) on PD were treated in the hospital. When only infection-related hospitalizations were taken into account, the adjusted IRRs for overall infection (1.21; 95% CI: 0.96-1.53) and dialysis technique-related infection (2.90; 95% CI: 2.09-4.19) were somewhat attenuated, whereas the IRR for non-dialysis technique-related infection (0.52; 95% CI: 0.34-0.75) did not change. In an unadjusted (HR: 1.36; 95% CI: 1.08-1.71) and adjusted Cox proportional hazard analysis (adjusted HR: 1.54; 95% CI: 1.18-2.02), the association between dialysis modality and infectious complications did not change substantially when only the first infection was taken into account. When a Cox proportional hazard model using dialysis modality as a time-dependent variable was performed the unadjusted (HR: 2.06; 95% CI: 1.48-2.88) and adjusted association (adjusted HR: 2.23; 95% CI: 1.53-3.25) between dialysis modality and infection was immunosuppressive therapy (PD: n=7; HD: n=21) were excluded from the analyses, estimated effects did not change (data not shown).
Chapter 2

Discussion

This cohort study of incident dialysis patients shows that PD patients are overall at a higher risk for infectious complications compared with HD patients. However, PD was associated with a lower risk for non-dialysis technique-related infections. This association was strongest within the first 6 months after the start of dialysis. After 6 months, the IRRs are not significant without any consistent trend. In both HD and PD patients, the infection incidence rate was highest 0-3 months after the initiation of dialysis and decreased later on. In the first 6 months of dialysis, HD patients had a higher age-standardized incidence rate of infections compared with PD patients, although this did not remain significant after further adjustment for confounding factors.

Our study has several strengths and weaknesses. Although the NECOSAD data was collected prospectively, we retrospectively collected data on infectious complications. A disadvantage of retrospective data collection is its dependency on accurate record keeping. However, we are confident that a thorough review of complete original medical records of 452 NECOSAD patients was performed. Most likely, infections of less severity may have been underreported, because they were not recorded or were treated by the general practitioner instead of the nephrologist. We attempted to limit this information bias by reviewing both in- and outpatient files, which allowed us to focus on infectious hospitalizations and infections of less severity treated by the nephrologist. Still, misclassification is probably differential for infections of less severity because PD patients are more likely to consult their general practitioner due to their home-based treatment. It is possible that this may have affected both infection rates and the comparison between modalities.

A major strength of the NECOSAD cohort is that it included a population of stable incident dialysis patients with a long follow-up period. In addition, we were able to follow patients from the start of renal replacement therapy, which was advantageous compared with the majority of previous studies that often excluded the first 90 days on dialysis, which is a high-risk period for infections. No protocol changes or care bundle approaches were introduced during the NECOSAD study period that might have influenced the infection rates over time. Our study has shown a 1.7-fold higher risk for infectious complications in PD patients. This is consistent with earlier findings in the United States Renal Data System database and the Canada Organ Replacement Register, although these studies only included infection-related hospitalizations and did not assess less severe infections. In other studies, no association between dialysis modality and overall infection-related hospitalization rates was observed, although a similar, but not significant trend towards a higher incidence rate on PD could be recognized. A study from Pittsburgh, USA, has shown no association between dialysis modality and overall infection rates. In the present study, the association with dialysis modality attenuated when only infection-related hospitalizations were taken into account.
towards a 1.2-fold higher risk for infection in PD patients, which was no longer significant. This may indicate that PD patients experienced more infections of less severity that did not require hospitalization compared with HD patients.

This study has shown that the increased risk for infectious complications in PD patients could be explained by a 4-fold higher risk for dialysis technique-related infections in PD compared with HD patients, like peritonitis and access infection. The risk for dialysis technique-related infections attenuated towards a threefold higher risk, when only infection-related hospitalizations were taken into account. Lafrance et al. have shown a similar adjusted hazard ratio of 3.5 for dialysis-related infections in a Canadian cohort. Interestingly, a 2-fold lower adjusted IRR for non-dialysis technique-related infections was observed in PD patients compared with HD patients, which did not change when the analysis was limited to infections treated in the hospital. Similar to others, we have shown that the incidence rates of respiratory infection and septicaemia are higher in HD patients. Although a well-substantiated pathophysiological explanation has not been elucidated, a number of hypotheses can be considered. The most straightforward hypothesis is that the association might be explained by a difference in underlying health status between HD and PD patients. Consistent with general clinical experience, HD patients were older and carried more comorbidities than PD patients. Although extensive adjustment for confounders was performed, residual confounding, in terms of confounding by indication, cannot be excluded due to the observational design of the study.

Some studies suggested that the difference in the incidence rate of pneumonia might be explained by the fact that HD patients are treated predominantly in a hospital setting whereas PD is a home-based treatment. If so, a high number of typically hospital-acquired microorganisms would be observed causing non-dialysis technique-related infections. However, this was not the case (data not shown).

A pathophysiological explanation of the observed differences between infection rates would be that some characteristics of the dialysis modalities influence the immune system and therefore alter the risk for infectious complications. Fluid overload, accumulation of uraemic toxins and a constant exposure to oxidative stress could have immunosuppressive effects. These effects might be enhanced in HD compared with PD patients, because HD patients are dialysed in an intermittent fashion, whereas PD results in a more continuous removal of fluid and uraemic toxins. Furthermore, it has been suggested that chronic systemic inflammation might alter the function of the immune system. Systemic inflammation in HD patients is induced by the contact of blood with bio-incompatible dialysis membranes and accumulation of uraemic toxins. However, in PD, inflammation can be induced by the bio-incompatible dialysate containing glucose and its degradation products. The presence of a better residual renal function in PD patients might temporarily prevent the induction of inflammation. For these reasons, several authors have speculated that the burden
Chapter 2

of systemic inflammation might be higher in HD patients compared with PD patients. The observation that HD patients have higher CRP levels when compared with PD patients provides support for such hypothesis.\(^3\)

Thus, previous evidence consistently supports the hypothesis that a true difference in non-dialysis technique-related infections exists. Both environmental factors and pathophysiological changes may contribute to this difference. We speculate that the association between dialysis modality and the immune system has the largest impact.

In this study, we described the incidence trend of infectious complications over time. A similar trend has been shown by Dalrymple \textit{et al.}\(^4\) in their United States Renal Data System-derived cohort of patients aged 65-100 years. The relatively higher risk for infections related to the vascular access in the early months on HD was consistent with previous results derived from North American cohorts.\(^2,3\) Previously, the dialysis outcomes and practice patterns study\(^41\) showed that still a large proportion of patients start dialysis with a central venous catheter. Using NECOSAD data, Ocak \textit{et al.}\(^24\) found that the use of central venous catheter at 3 months after the start of dialysis increased the risk for infection-related mortality as compared with arteriovenous access use among elderly patients. We demonstrated that a central venous catheter and an arteriovenous graft are associated with an increased risk for dialysis technique-related infections among HD patients. Therefore, the elevated early risk in HD patients could possibly be diminished by timely preparation of a permanent vascular access, like an arteriovenous fistula. Although a reasonable explanation, we can only speculate whether insufficient access preparation in HD patients might be the explanation for our findings directly after the start of dialysis. Unfortunately, data on the type of vascular access at the baseline of the study and updated information about vascular access were not available in our patients.

In conclusion, our study demonstrated that PD patients are at higher risk for infectious complications compared with HD patients. This difference can be explained by peritonitis and access infections, occurring as a complication of PD. Furthermore, our study confirmed and extended previous findings that suggested an increased risk for non-dialysis technique-related infections in HD patients, like pneumonia. The pathophysiological link between dialysis modality and the immune system may explain the difference in non-dialysis technique-related infection risk between HD and PD patients. However, further studies are needed to test the assumptions and identify the most important ones. We feel that early and intensive counseling is needed for every patient to make a timely modality decision resulting in on-time preparation for the modality of choice and potential prevention of infectious events. Furthermore, during the counseling for dialysis, substantial attention should be paid to preventative measures for infectious events.
Acknowledgements

We thank the trial nurses, participating dialysis centers and data managers of the NECOSAD study for collection and management of the data. We gratefully thank all patients who participated in the NECOSAD study. This work was supported by an ERA-EDTA short-term fellowship grant (STF-124). The ERA-EDTA was not involved in the collection, interpretation and analysis of the data, or in the decision for writing and submitting this report for publication.
References


Chapter 3

Protein-energy wasting is a risk factor for infections in both hemodialysis and peritoneal dialysis patients

Anouk T.N. van Diepen, Tiny Hoekstra, Renée de Mutsert, Joris I. Rotmans, Mark G.J. de Boer, Marit M. Suttrop, Dirk G. Struijk, Els W. Boeschoten, Raymond T. Krediet, Friedo W. Dekker

Submitted for publication
Abstract

Background and objectives: Protein-energy wasting (PEW) has been linked to impaired immunity in both peritoneal dialysis (PD) and hemodialysis (HD) patients. The objective of our study was to investigate the association between protein-energy wasting and the risk of infections in both HD and PD patients.

Design, setting, participants, and measurements: In a prospective multi-center cohort study of incident dialysis patients (NECOSAD), the 7-point Subjective Global Assessment of nutritional status (SGA) was assessed every six months. Information about infections of all patients from 5 participating hospitals was retrospectively collected from the start of dialysis until censoring or 3 years of follow-up. PEW was defined as SGA 1-5. Incidence rate ratios (IRR) were calculated with (time-dependent) Poisson regression considering all infections in 3 years of follow-up. Models were adjusted for age, sex, ethnicity, primary kidney disease, smoking and comorbidity.

Results: This study included 400 patients, of whom 240 initially started on HD and 160 on PD. Thirty-two percent of HD patients and 18% of PD patients suffered from PEW at dialysis start. Both HD (Adjusted IRR: 1.42; 95% CI: 1.09-1.97) and PD patients (1.37; 0.98-1.92) suffering from PEW showed an increased risk for infection compared with patients with a normal nutritional status. Compared with HD patients with a normal nutritional status (reference group), adjusted IRRs for infection were 1.81 (95% CI: 1.41-2.32) for PD patients with a normal nutritional status, 1.42 (1.09-1.97) for HD patients with PEW, and 2.45 (1.71-3.50) for PD patients with PEW.

Conclusions: PEW was associated with an increased risk of infection in both HD and PD patients. Routine screening of nutritional status is important in all dialysis patients.
Introduction

Protein-energy wasting (PEW) is a state of decreased body stores of protein and energy stores.\(^1\) The prevalence of PEW in dialysis patients varies widely and depends strongly on the method of assessment and the population studied. Reported prevalences range between 10-76% in hemodialysis (HD)\(^2-15\) patients and 10-50% in peritoneal dialysis (PD) patients.\(^1\) Previous reports suggest that wasting of protein and energy stores facilitates the weakening of the barrier function to invading pathogens.\(^19-21\) In chronic dialysis patients, PEW has been linked to impaired barrier function of the innate and adaptive immune system.\(^19,22,23\) Decreased immunogenic function of polymorphonuclear leukocytes,\(^24,25\) T-lymphocytes,\(^20,21,26\) monocytes and monocyte-derived dendritic cells\(^27\) has been observed in dialysis patients with PEW when compared with dialysis patients with a normal nutritional status. Therefore, it has been hypothesized that dialysis patients suffer from increased susceptibility to infections subsequent to PEW.\(^28\)

Infections are a major cause of morbidity and mortality in both HD and PD patients.\(^29-31\) In a previous study\(^32\) we investigated the association between the initial dialysis modality and the risk of dialysis technique and non-dialysis technique-related infections. Consistent with earlier reports,\(^33,34\) we have demonstrated that PD patients have a higher baseline risk of infections, predominantly explained by peritonitis and exit site infections. In contrast, HD patients appear to have a higher risk of infections that could not be attributed to the dialysis technique, such as pneumonia. The latter observation may be a consequence of a worse underlying health status, possibly linked to PEW. Therefore, the objective of our study was to investigate the association between PEW and the risk of all-cause and cause specific infectious complications in HD and PD patients.

Methods

Design and population

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study is a multicenter prospective cohort study of dialysis patients from 38 centers in The Netherlands. Incident end-stage renal disease (ESRD) patients, aged ≥18 years, starting dialysis between 1 January 1997 and 1 January 2007 were eligible for inclusion. Medical ethics committees of all participating hospitals approved the study. All participants gave their written informed consent. For the present study, detailed information about infections was adjudicated from both in- and outpatient medical records of all 471 patients from five dialysis centers that participated in NECOSAD: two tertiary care university hospitals and three regional hospitals. These dialysis centers were chosen for practical reasons (travel distance and the number
of included patients). Follow-up started at three months after start of dialysis, because the first classification of the nutritional status was performed at the 3-months study visit. Time of follow-up was defined as the number of days between the 3-months study visit and the date of censoring due to death, modality switch, withdrawal from the study, transfer to a dialysis center not participating in NECOSAD, kidney transplantation, at the end of the study follow-up period in (June 2009), or at a maximum follow-up of three years.

Descriptive data
Routine collected demographic and clinical data at the dialysis centers included dialysis modality, age, sex, ethnicity, primary kidney disease, comorbid conditions, Kahn comorbidity score (low, medium, high), body mass index (BMI) in four categories, medication, smoking status, C-reactive protein (CRP), hemoglobin and serum albumin. Primary kidney disease was classified according to the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) codes and grouped into four categories.

Subjective global assessment
Nutritional status was assessed with the 7-point subjective global assessment (SGA) at three months and at six months and subsequently at intervals of six months until the end of follow-up. The 7-point SGA is a modification of the originally described 3-point SGA scale and has been validated in the NECOSAD cohort. Before the start of NECOSAD, the research nurses of the participating dialysis centers were trained to assess the SGA using a structured scoring form according to a standardized protocol. These trained research nurses scored the history of weight change during the previous 6 months (subscale 1), dietary intake, and presence of gastro-intestinal symptoms (subscale 2), and conducted a physical examination of loss of subcutaneous fat mass (subscale 3) and muscle wasting (subscale 4) (see appendix 2 in chapter 10 of this thesis). The criteria for scoring these subscales were similar to those described in detail by Detsky and collugues. Based on weighting of the scores of these subscales, the research nurses appointed the SGA classification of 1–7: 1–3 indicating severe PEW, 4–5 moderate PEW and 6–7 a normal nutritional status.

Infections
Data on infectious complications were retrospectively collected from the start of dialysis until death or censoring using pre-specified criteria. An infection was considered present when 1) written diagnosis of a nephrologist or other physician is present, and 2) supported by evidence such as a positive culture, radiologic confirmation, or antibiotic, antiviral, or antifungal treatment. In case of a soft tissue infection, a respiratory tract infection other than pneumonia and in the case of urinary tract infections, for the diagnosis treatment was required. All infections were further classified as dialysis technique-related infection (access
infection, vascular access associated sepsis, peritonitis) and non-dialysis technique-related infections (all other infections).

**Statistical analyses**
Baseline characteristics were stratified according to the SGA classification and by dialysis modality. Continuous data are expressed as mean and standard deviations or median and interquartile ranges (IQR) and categorical variables in proportions. Differences between baseline characteristics were tested with an unpaired Student’s t-test, Mann-Whitney or chi-square test. All analyses were performed in HD and PD patients separately. Poisson regression models were used to calculate incidence rate ratios (IRRs) with 95% confidence intervals for infections. We performed these analyses with the patients grouped into 2 SGA categories, 1-5 indicating protein-energy wasting and 6-7 indicating a normal nutritional status, using the latter as reference. Analyses were adjusted for baseline measurements of age, sex, ethnicity, primary kidney disease, Kahn co-morbidity score and smoking. Because nutritional status may vary over time on dialysis, we calculated time-dependent IRRs of infection. In these analyses, additional adjustments were made for the number of infections during the previous 6 months. Next, the combined association of PEW and dialysis modality with infection risk was assessed. We compared patients without PEW on PD, with PEW on HD and with PEW on PD to HD patients without PEW as the reference category. The results are presented following the STROBE reporting guideline for effect modification. Furthermore, we calculated the time-dependent IRRs of the association between the classification on the four subscales of the SGA and infections, using an SGA score of 1 as the reference category. Also, a time-dependent analysis was performed using changes in SGA during the preceding 6-month time interval as exposure, using “no change” as the reference. In this analysis, additional adjustments were made for the SGA classification at the previous study visit. Although the data are rather complete, missing values were imputed with multiple imputation techniques using chained equations (MICE) in STATA with 10 imputation data sets. All data analyses were performed using SPSS 20.0 and STATA 12.1.

**Sensitivity analyses**
Analyses were repeated without the additional adjustments in the time-dependent analyses and the analyses concerning the change in SGA classification, because they might be in the causal pathway. Since weight change is an important component of the SGA, sensitivity analyses were performed to assess the association between BMI (in four categories) and infection risk. Analyses were repeated after exclusion of patients using immunosuppressive therapy. An adjusted Cox proportional hazard model was used to evaluate whether the results would change when only the first infection was taken into account.
Chapter 3

Results

Population characteristics
Medical records of all 471 NECOSAD patients from the 5 centers were reviewed. Patients with incomplete or lost files (n=19) were excluded from the study. Between the start of dialysis and 3 months 52 patients died or were censored. Therefore, at the 3-months study visit, 400 patients still participated in the study and were included in the present analysis. When compared with the complete NECOSAD study cohort, the patients included in this study had similar baseline characteristics (data not shown). The baseline characteristics of the study population are summarized in Table 1. In total, 240 patients were treated with HD and 160 with PD. Thirty-two percent of HD patients (n=76) and 18% of PD patients (n=27) suffered from PEW at baseline. Dialysis patients suffering from PEW were somewhat older, had a lower BMI and appeared to have more co-morbid conditions then those with a normal nutritional status. The median follow-up time was 1.9 years (IQR: 0.4-2.8) on HD with PEW, 1.6 years (IQR: 0.6-2.8) on HD with a normal nutritional status, 1.7 years (IQR: 0.4-2.8) on PD with PEW and 1.4 years (IQR: 0.2-2.8) on PD with a normal nutritional status. In total, HD patients with and without PEW experienced 84 and 135 infections. PD patients with and without PEW suffered from 48 and 184 infections. The incidence of infection was 0.68 per dialysis year on HD with PEW, 0.46 per dialysis year on HD without PEW, 1.16 per dialysis year on PD with PEW and 0.78 per dialysis year on PD without PEW.

PEW and infections
Crude and adjusted IRRs for the association between PEW and the 3-years and time-dependent incidence of infection are shown in Table 2. Compared with patients without PEW at baseline, in both HD and PD patients, PEW was associated with a 40% increased 3-years risk to develop all-cause infections. The time-dependent IRRs for all-cause infection were even stronger. Also, the 3-years IRR of dialysis technique-related infections was elevated in both HD patients with PEW (Adjusted IRR: 1.31; 95% CI 0.74-2.32) and PD patients with PEW (1.51; 1.04-2.19) when compared with patients with a normal nutritional status at baseline. We observed an increased 3-year IRR of non-dialysis technique-related infections in HD patients who suffered from PEW (1.48; 1.05-2.10), but not in PD patients with PEW (0.98; 0.44-2.18). The time-dependent risk of non-dialysis technique related infections was increased in HD patients (1.77; 1.25-2.52) but not in PD patients. The latter group suggested an 18% increased incidence of infection in those with PEW when compared with PD patients with a normal nutritional status, but the confidence interval around the estimate is rather wide.
## Table 1. Baseline characteristics of the study population, stratified by dialysis modality and nutritional status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD patients</th>
<th>PD patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PEW&lt;sup&gt;£&lt;/sup&gt;</td>
<td>Normal nutrition&lt;sup&gt;£&lt;/sup&gt;</td>
</tr>
<tr>
<td>Patients (n)</td>
<td>76</td>
<td>164</td>
</tr>
<tr>
<td>Age start dialysis&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>71.1 (64.0-75.7)</td>
<td>69.1 (57.2-75.1)</td>
</tr>
<tr>
<td>Men (%)</td>
<td>68</td>
<td>62</td>
</tr>
<tr>
<td>Ethnicity (% Caucasian)</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)&lt;sup&gt;§&lt;/sup&gt;</td>
<td>23.7 (4.4)</td>
<td>25.7 (3.9)</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes* (%)</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Malignancy (%)</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>57</td>
<td>48</td>
</tr>
<tr>
<td>Kahn co-morbidity score (% high)</td>
<td>45</td>
<td>40</td>
</tr>
<tr>
<td>Primary kidney disease (%)</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Renal Vascular disease</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>Past smokers</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)&lt;sup&gt;§&lt;/sup&gt;</td>
<td>6.6 (1.0)</td>
<td>6.8 (0.8)</td>
</tr>
<tr>
<td>Serum albumin (g/L)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>32.9 (10.9)</td>
<td>32.6 (6.0)</td>
</tr>
<tr>
<td>CRP (mg/L)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>8 (3-19)</td>
<td>6 (3-15)</td>
</tr>
<tr>
<td>nPCR (g/kg/day)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>0.80 (0.63-0.97)</td>
<td>0.86 (0.76-1.00)</td>
</tr>
</tbody>
</table>

Abbreviations: HD: hemodialysis; ESRD, End-stage renal disease; PEW, Protein-energy wasting; IQR, Interquartile range; *both diabetic nephropathy and diabetes as comorbidity; £ SGA-classification 1-5; ¥ SGA-classification 6,7; § values represent: mean (SD); ¶ values represent: median; IQR.
### Table 2. Association between protein-energy wasting and 3-years and time-dependent IRRs for infection on dialysis

<table>
<thead>
<tr>
<th></th>
<th>All-cause infection</th>
<th>Dialysis technique-related infections</th>
<th>Non-dialysis technique-related infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-years IRR</td>
<td>Time-dependent IRR</td>
<td>3-years IRR</td>
</tr>
<tr>
<td><strong>HD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.57 (1.18-2.08)</td>
<td>2.37 (1.79-3.15)</td>
<td>1.63 (0.97-2.73)</td>
</tr>
<tr>
<td>Adjusted model 1*</td>
<td>1.47 (1.11-1.95)</td>
<td>2.13 (1.59-2.84)</td>
<td>1.60 (0.95-2.71)</td>
</tr>
<tr>
<td>Adjusted model 2**</td>
<td>1.42 (1.09-1.97)</td>
<td>1.76 (1.30-2.37)</td>
<td>1.31 (0.74-2.32)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.42 (1.03-1.96)</td>
<td>1.72 (1.21-2.44)</td>
<td>1.58 (1.11-2.26)</td>
</tr>
<tr>
<td>Adjusted model 1*</td>
<td>1.42 (1.03-1.96)</td>
<td>1.71 (1.20-2.44)</td>
<td>1.54 (1.07-2.20)</td>
</tr>
<tr>
<td>Adjusted model 2**</td>
<td>1.37 (0.98-1.92)</td>
<td>1.56 (1.08-2.24)</td>
<td>1.51 (1.04-2.19)</td>
</tr>
</tbody>
</table>

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; IRR, IRR; SGA-classification was updated every time-dependent; Protein-energy wasting, defined as SGA 1-5 compared with SGA 6-7 as the reference group; *adjusted for age, Kahn comorbidity-score ** + sex, primary kidney disease, ethnicity and smoking; for the time-dependent analysis + number of infections during the previous 6 months.
The combined effect of PEW and dialysis modality on infection risk

Table 3 shows the combined effects of PEW and dialysis modality on infection risk. Both PD patients with a normal nutritional status and HD patients with PEW had a higher risk of infection compared with HD patients with a normal nutritional status. The combined effect was somewhat, but not substantially, higher than the sum of the separate risks (2.45; 1.71-3.50). In addition, the IRR for PEW in the PD stratum (1.37; 0.98-1.92) and the IRR for PEW in the HD stratum (1.42; 1.09-1.97) were similar. Therefore, the association of PEW with infection is not different across strata of dialysis modality.

Table 3. Combined risks of protein-energy wasting and dialysis modality on infection

<table>
<thead>
<tr>
<th>Normal nutritional status</th>
<th>Protein-energy wasting&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>N with/without infection</td>
<td>IRRs (95% CI)</td>
</tr>
<tr>
<td>HD</td>
<td>119/45</td>
</tr>
<tr>
<td>PD</td>
<td>103/30</td>
</tr>
</tbody>
</table>

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; *protein-energy wasting was defined as SGA 1-5; *adjusted for age, Kahn comorbidity score, sex, ethnicity, primary kidney disease, smoking status.

SGA subscales and risk of infections

Crude and adjusted time-dependent IRRs for the association between the SGA subscales and subsequent infections, in strata of dialysis modality, are shown in Figure 1. In both HD and PD patients, each point higher classification on all SGA subscales was associated with a decreased all-cause, dialysis technique-related and non-dialysis technique-related infection risk during the next 6 months. Higher SGA subscale classifications of intake and GI symptoms, loss of fat mass and muscle wasting resulted in significantly lower IRRs of infection, whereas a higher subscale classification of weight change appeared to be of less influence.

The change in SGA and the subsequent risk of infections within the next 6 months

Crude and adjusted time-dependent IRRs for the association between the change in SGA classification during the preceding 6 months and infection incidence within the next 6 months in strata of dialysis modality, are shown in Table 4. With every one point increase in SGA classification, the IRR of all-cause infection during the next 6 months was 17% lower in HD and 29% lower PD patients. In HD patients, both the IRR of dialysis technique-related infection (0.65; 0.47-0.91) and the IRR of non-dialysis technique-related infections (0.53; 0.43-0.67) were lower with one point increase in SGA during the preceding 6 months. A similar effect was seen in PD patients (dialysis technique-related infections: 0.77; 0.56-1.06, non-dialysis technique-related infections: 0.53; 0.31-0.93).
Table 4. Association between the change in SGA during the previous 6 months and the time-dependent \(^6\) IRR for infections \(^5\)

<table>
<thead>
<tr>
<th></th>
<th>All-cause infections</th>
<th>Dialysis technique-related infections</th>
<th>Non-dialysis technique-related infections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD</td>
<td>PD</td>
<td>HD</td>
</tr>
<tr>
<td>Crude</td>
<td>1.04 (0.86-1.27)</td>
<td>0.85 (0.70-1.04)</td>
<td>0.86 (0.59-1.26)</td>
</tr>
<tr>
<td>Adjusted*</td>
<td>0.84 (0.69-1.01)</td>
<td>0.73 (0.59-0.91)</td>
<td>0.61 (0.44-0.86)</td>
</tr>
<tr>
<td>Adjusted**</td>
<td>0.83 (0.68-1.00)</td>
<td>0.71 (0.58-0.89)</td>
<td>0.65 (0.47-0.91)</td>
</tr>
</tbody>
</table>

Abbreviations: HD, hemodialysis; PD, peritoneal dialysis; IRR, IRR; \(^6\)SGA-classification was updated time-dependent; \(^5\)infection risk per one point increase in SGA classification during the preceding 6 months; \(^*\)IRRs were adjusted for age, comorbidity-score, sex, primary kidney disease, ethnicity, smoking and the number of infections during the previous 6 months; \(^**\)previous SGA-value at the start of previous time-dependent time point.
Sensitivity analyses
Without the additional adjustments the estimates did no change (data not shown). The association between BMI and infections was less consistent than between SGA and infections, mainly due to the small number of patients in the extreme categories (approximately 5% with a BMI <18.5 and 10% with a BMI ≥30). When using a BMI of 18.5-24.9 kg/m² as the reference category, in HD patients with a BMI of <18.5, 25.0-29.9 or ≥30 kg/m², the adjusted associations with infections were 1.07 (0.42-2.76), 1.11 (0.79-1.56) and 1.49 (0.97-2.29). In PD patients, these associations were 5.39 (1.58-18.41), 0.67 (0.50-0.90) and 0.97 (0.63-1.50). When patients who received immunosuppressive therapy (n=28) were excluded from the analyses, estimated effects were similar (data not shown). In an adjusted Cox proportional hazard analysis, the association between PEW and time to the first infection was comparable in HD (HR: 1.64; 95%CI: 1.16-2.32) and PD patients (1.33; 0.84-2.12).

Figure 1. Association between the SGA classification on the four subscales and the time-dependent IRRs* with 95% confidence intervals for infections.
●: all-cause infection; ▲: dialysis technique-related infection; ■: non-dialysis technique-related infection. ¶Association per point higher on the SGA subscale; SGA-classification =1 is the reference §SGA-classification on the subscale was updated time-dependent. *IRRs were adjusted for age, comorbidity-score, sex, primary kidney disease, ethnicity, smoking and the number of infections during the previous 6 months

Discussion
The results of this cohort study showed that PEW, represented by an SGA-score of 1-5, was associated with a 40% increased risk of infections in both HD and PD patients. Moreover, the time-dependent associations were even stronger as an indication of the short-term risk of PEW. Our study also showed that recent improvement of the patients’ SGA classification was associated with a lower subsequent 6-months risk of infections. Furthermore, of the four SGA subscales, “intake and GI symptoms”, “loss of fat mass” and “loss of muscle mass” were stronger associated with infections than “weight loss”. More importantly, each point higher on any SGA subscale was associated with a decreased risk of infection.
In addition, we assessed whether PEW would have a different association with infection in patients on HD or on PD. Our results showed that the association of PEW with infection is not different across strata of dialysis modality. We previously have shown that the baseline risk of overall infection on dialysis is higher in PD patients compared with HD patients. Also in the present study, in absolute numbers, both PD patients with and without PEW developed more infections than HD patients with and without PEW. However, the relative influence of PEW on the infection risk is similar in both modalities.

In PD patients, only a trend towards an association with non-dialysis technique-related infection on the short-term could be observed. It suggests that PEW is a less important trigger for the development of a non-dialysis technique-related infection in the PD patient. However, the confidence interval around the estimate was rather wide, which may be caused by the small number of PD patients with PEW that develop non-dialysis technique-related infections.

The present study has several strengths and weaknesses. Although patients in the NECOSAD data were followed prospectively, we retrospectively collected data on infections. However, we are confident that a thorough review of complete original medical records was performed using strict, pre-specified criteria. Second, infections of less severity may have been underreported, because they were not recorded or were treated by the general practitioner instead of the nephrologist. We attempted to limit this information bias by reviewing both in- and outpatient files. Third, since the first classification of the nutritional status by SGA was performed at the 3-months study visit, follow-up started 3 months after the start of dialysis. Therefore, a period with a high infection incidence rate was excluded from our analyses. Fourth, the number of patients with an SGA classification of 1 and 2 was very low. As a consequence, we were unable to make a distinction between moderate and severe PEW. Therefore, our findings might underestimate the effects in patients with severe PEW. A major strength of the NECOSAD cohort is that it contains a population of incident dialysis patients with a long-term follow-up. A specific strength of NECOSAD is that patients underwent structural 6-monthly SGA measurements performed by trained research nurses. In our study, patients with an SGA classification of 1-5 at baseline were older and had more co-morbid conditions then those with a normal nutritional status. Although extensive adjustments were made, residual confounding cannot be excluded due to the observational design of the study. However, it is unlikely that unknown or imperfectly measured confounders completely explain the observed increased IRRs for infection in patients with PEW.

To the best of our knowledge, the present study is the first to associate PEW, defined by SGA classification, with an increased risk of infections in patients on dialysis. Studies from other medical specialties have established the association between malnutrition...
and infection for many years. In 2013, the International Society for Renal Nutrition and Metabolism (ISRNM) acknowledged infection both as a cause and a potential consequence of PEW in dialysis patients. More recently, the ISRNM stated that the increased infection incidence rate in patients with chronic kidney disease might not only be a result of uremic immunodeficiency but also a consequence of an interaction between PEW and the immune system. In dialysis patients, evidence about the association between PEW, immunity and infection is scarce. More research, to differentiate between the effects of uremia, catabolic effects of the dialysis treatment itself and PEW on the immune system is necessary. Although alternative nutritional scores and technical body composition examinations have been developed, one of the most valid and reliable clinical parameters for assessment of nutritional status remains the 7-point SGA. The strength of the SGA is its combination of medical history taking and physical examination. When BMI was used as parameter of PEW, the association with infection was less consistent. This might have been due to the small number of patients in the extreme categories. The disadvantage of BMI is its inability to differentiate between fat and muscle mass and that it does not discriminate between central or peripheral fat distribution, whereas SGA has the advantage that it can provide distinct information about loss of fat and muscle mass. Our study showed that, in addition to weight change, intake and GI symptoms and loss of fat and muscle mass are even stronger associated with the risk of infection. Therefore, we feel that a single BMI measurement does not provide sufficient information about the nature of the weight change and subsequent infection risk. Our results underline that the SGA is an important risk factor not only with respect to mortality, but also for infection.

In conclusion, our cohort study demonstrated that PEW, classified by the SGA, is associated with an increased risk of infections. Our results underline that the SGA is a valuable measurement not only in association with mortality, but also with infection. Future studies are needed to improve our knowledge about the influence of PEW, apart from uremic immunodeficiency and the catabolic characteristics of the dialysis procedure. Intervention studies focussing on the improvement of SGA classification are needed to establish whether a decrease of infection risk can be achieved by an improvement of the nutritional status of dialysis patients.

Acknowledgements

We thank the trial nurses, participating dialysis centers and data managers of the NECOSAD study for collection and management of the data. We gratefully thank all patients who participated in the NECOSAD study. The authors would like to acknowledge Saskia Le Cessie, PhD, for her valuable statistical advice. This work was supported by an ERA-EDTA short-term
fellowship grant (STF-124). The ERA-EDTA was not involved in the collection, interpretation and analysis of the data, or in the decision for writing and submitting this report for publication. An abstract submitted to the 51st ERA-EDTA conference was published (Abstract SP684. *Nephrol Dial Transplant* 2014; 29 (Suppl 3): iii287-iii303).
References


Chapter 4

The association between exit site infection and subsequent peritonitis among peritoneal dialysis patients

Anouk T.N. van Diepen, George A. Tomlinson, Sarbjit V. Jassal

Clinical Journal of the American Society of Nephrology 2012
Volume 7, pages 1266-1271

Abstract

Background and objectives: Peritonitis is the most common infectious complication seen in peritoneal dialysis (PD). Traditionally, exit site infection (ESI) has been thought to predispose to PD peritonitis, although the risks have not been quantified. This study aimed to quantify the risk of PD peritonitis after ESI.

Design, setting, participants, & measurements: Data from 203 clinically stable PD patients >18 years of age who were followed as part of a randomized controlled trial over 18 months were used to estimate the risk of developing peritonitis within 30 days of an ESI compared with individuals who did not have recent ESI. Sensitivity analyses were performed at 15, 45 and 60 days.

Results: Patients were mostly male (64.5%) and Caucasian, with a mean age of 60.5 ± 14.4 years. There were 44 ESIs and 87 peritonitis episodes during the 18-month study. Seven patients had an ESI followed by peritonitis within 30 days. Using a frailty model, patients who had an ESI had a significantly higher risk of developing peritonitis within 30 days, even if the ESI was appropriately treated (HR=6.3, 95% CI=2.9-14.0). This risk was maximal early on and diminished with time, with hazard ratios (95% confidence interval) of 11.1 at 15 days (HR=11.1, 95% CI=4.9-25.1), 5.3 at 45 days (2.5-11.3), and 4.9 at 60 days (2.4-9.9). In 2.3% of patients, subsequent peritonitis was caused by the same organism as the previous ESI.

Conclusions: A strong association between a treated exit site infection and subsequent PD peritonitis was present up to 60 days after initial diagnosis.
Introduction

Treatment-related infections, such as peritonitis, continue to be the leading cause of morbidity and mortality in peritoneal dialysis (PD) patients. In addition, PD-related infection is the most common cause of technique failure.1-5 Much effort is placed on the prevention of peritonitis and the avoidance of the resulting severe complications.4-6 Traditionally, it has been thought that exit site infection (ESI) increases the risk of peritonitis via transmigration of organisms from the exit site along the PD catheter tunnel into the peritoneal cavity.3-6 Earlier studies that suggest a relationship between ESI and peritonitis have been largely retrospective or conducted using data from prospective observational cohorts or databases, with the majority being published before 2000. Although most of these studies have been consistent with the premise that an ESI places a PD patient at increased risk of peritonitis,7-27 none have quantified the strength of the reported relationship nor defined the period of time after ESI that was associated with increased peritonitis risk. Furthermore, in recent years, the spectrum of organisms causing infections in the PD population has changed, with a significantly higher proportion of Gram-negative organisms being seen due in part to a decline in infections with skin organisms.28-30 International Society for Peritoneal Dialysis (ISPD) guidelines have led to a wider use of topical antibiotic prophylaxis at the catheter exit site and more aggressive management of ESIs.31-35 We therefore hypothesized that the relationship between ESI and peritonitis might no longer be seen in a contemporary cohort of patients. We used data collected as part of a blinded multicenter randomized controlled trial (RCT)36 to assess if a temporal relationship between ESI and peritonitis truly exists and to quantify the risks in both those treated with systemic and nonsystemic therapy for their ESI.

Materials and methods

Patients

Data were extracted from a multicenter RCT comparing two PD catheter exit site ointments, mupirocin and Polysporin Triple.36,37 Patients were taught to apply the study ointment to the exit site with each dressing change. All aspects of medical care, including exit site care, dressing change frequency, dialysis protocols, and management of PD-related infections, were left to discretion of the patient’s primary nephrologist. All ESIs and peritonitis episodes were recorded prospectively as part of the study protocol using rigorous methods (ongoing direct patient contact and review of all dialysis unit logs and charts as well as formal study incident reports). As per local training procedures, patients were reminded to contact their dialysis team if either exit site infection or peritonitis was suspected. This included data on
microbiology of ESI and peritonitis episodes as well as treatment for these infections. The choice of treatment for ESIs was left to the physician’s discretion. Trial results showed no significant decrease in PD-related infections with the routine use of Polysporin Triple at the exit site.\(^7\)

**Definitions**
The ISPD definitions were used.\(^3^5\) ESIs were defined as purulent drainage from the exit site with or without erythema. Peritonitis was defined as the presence of two of the following three findings: abdominal pain, cloudy effluent with \(\geq 100\) white blood cells/\(\mu\)L and \(\geq 50\%\) polymorphonuclear cells, or positive microbiological culture of dialysate fluid. ESI and peritonitis were considered to be associated with each other if peritonitis followed within 30 days of the diagnosis of an ESI. In addition, sensitivity analyses for 15, 45 and 60 days were performed. Treatments of the ESI were classified as systemic (oral, intravenous or intraperitoneal antibiotics) or nonsystemic (topical antibiotics or other localized treatments).

**Statistical Analysis**
A Cox proportional hazards model was used to assess the relationship between ESI and peritonitis, with a frailty term to account for repeated episodes of peritonitis in each person. Each person was considered at baseline risk of an episode of peritonitis between the beginning and the end of the study period. We used a time-dependent variable for ESI, in which the first 30 days following an ESI were considered “exposed” to additional risk due to concomitant ESI. The variables for age, sex and presence of diabetes were included as covariates. The 30 days after ESI were considered as an “additional risk time period”, whereas the remaining time and time in subjects who did not have an ESI were considered as “baseline peritonitis risk period”. In addition, sensitivity analyses were performed using time epoch methodology\(^3^8\) and by using the time for ESI-related risk as 15, 45 and 60 days after an ESI. Crude rates of peritonitis (episodes per 100 days) in the time after ESI and the ESI-free time were reported.

**Prespecified secondary analyses**
Three pre-specified secondary analyses were performed. First, time dependency was assessed by performing the analysis using 15, 45 and 60 days after an ESI for the period of time at risk. Second, the analysis was limited to those episodes of peritonitis that occurred with identical organisms to that seen causing the ESI, based on the cultured organism. For the purpose of the analysis organisms were condensed into 8 groups: *Streptococcus* spp., *Staphylococcus aureus*, other Gram-positive organisms, *Pseudomonas* spp., other Gram-negative organisms, *Candida* spp., other organisms, and culture negative. Finally, the effect of exit site treatment was explored. Patients who were treated with oral, intravenous, or
intraperitoneal therapy were said to have received systemic therapy, whereas those who had been managed with only topical therapies were said to have received nonsystemic therapy.

**Results**

**Population characteristics**
The study population consisted of 203 PD patients, both incident (n=63) and prevalent (n=140). The demographic and baseline clinical characteristics of the study population are summarized in Table 1.

**Table 1. Demographic and baseline clinical characteristics of the study population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>203</td>
</tr>
<tr>
<td>Male (n (%))</td>
<td>131 (65%)</td>
</tr>
<tr>
<td>Age (yrs) ± SD</td>
<td>60.5 ± 14.4</td>
</tr>
<tr>
<td>Diabetic</td>
<td>88 (43%)</td>
</tr>
<tr>
<td>On immunosuppressive drugs at study start</td>
<td>22 (11%)</td>
</tr>
<tr>
<td>Peritoneal dialysis technique</td>
<td></td>
</tr>
<tr>
<td>Prevalent</td>
<td></td>
</tr>
<tr>
<td>APD</td>
<td>78 (39%)</td>
</tr>
<tr>
<td>CAPD</td>
<td>60 (29%)</td>
</tr>
<tr>
<td>Incident</td>
<td></td>
</tr>
<tr>
<td>APD</td>
<td>29 (14%)</td>
</tr>
<tr>
<td>CAPD</td>
<td>36 (18%)</td>
</tr>
</tbody>
</table>

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis

Most patients were male (64.5%) with a mean age of 60.5 ± 14.4 years (range, 22.8-96.6). Patients were on PD for a median time of 9.7 months (25<sup>th</sup> and 75<sup>th</sup> percentiles: 2.1 and 28.5 months, respectively). Demographic data are shown in Table 1. The patients were followed prospectively for a total of 2756 patient-months (median 18 months; range, 0.1 to 18.0 months), and 173 patients (85.2%) completed 18 months of follow-up or were followed up to catheter removal or death. The total follow-up after ESI was 271 months (median 6.3; range, 1-17 months).

**Incidence**
Thirty-four patients experienced 44 ESIs during the study period (overall exit site rate: 1 episode per 62.6 patient-months; 0.19 episodes per patient-year). ESIs were treated using systemic (*i.e.*, oral, intravenous or intraperitoneal) antibiotic in 18 patients (41.1%),
a combination of systemic antibiotics with modified topical therapy in 2 patients (4.5%), or nonsystemic therapies such as topical ointments or hydrogen peroxide in 24 patients (54.4%). Eight patients with ESIs received multiple systemic antibiotics. Peritonitis occurred in 57 individuals experiencing a total of 87 episodes (overall peritonitis rate: 1 episode per 31.7 patient-months, 0.38 episodes per patient-year). Causative organisms are shown in Table 2. The predominant organisms causing ESI and peritonitis were skin organisms. A negative culture occurred more frequently in peritonitis than in ESI. Five ESIs (11.4%) and 17 peritonitis episodes (19.5%) were culture negative. The single episode of peritonitis following an ESI that had the identical organism occurred with a *Corynebacterium* infection in which peritonitis occurred 1 week after ESI. The ESI was originally treated with increased dressing changes and topical hydrogen peroxide but no antibiotic.

**Risk of developing peritonitis after a recent ESI**

A strong association was found between a recent ESI and the development of subsequent peritonitis. The association was present after adjustment for age, sex, and presence of diabetes. Of the 44 ESIs, 7 were followed by subsequent peritonitis within 30 days and 12 within 60 days. The risk of developing peritonitis declined with time. Maximal risk was seen within 15 days of ESI, with a hazard ratio (HR) of 11.1 (95% confidence interval (CI), 4.9-25.1; *p*<0.001). The risk became attenuated with time; however, it remained clinically important up to 60 days after the onset of an ESI, with HRs of 6.3 at 30 days (95% CI, 2.9-14.0; *p*<0.001), 5.3 at 45 days (95% CI, 2.5-11.3; *p*<0.001), and 4.9 at 60 days (95% CI, 2.4-9.9; *p*<0.001) (Figure 1). Further assessment of the risk estimate at 90 and 120 days was not possible due to the relatively small number of ESI events.

![Figure 1: Risk of peritonitis over time after exit site infection, adjusted for age, race, and sex. Abbreviations: CI, confidence interval; ESI, exit site infection.](image_url)
Table 2. Detailed microbiology of ESIs and peritonitis events

<table>
<thead>
<tr>
<th>Organism</th>
<th>ESI P3</th>
<th>Mupirocin</th>
<th>Peritonitis P3</th>
<th>Mupirocin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Diptheroid spp.</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><em>S. epidermis</em></td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Coagulase negative <em>Staphylococcus</em> (excluding <em>S. epidermis</em>)</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><em>Streptococcus</em>, other</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Serraria</em> spp.</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td><em>Citrobacter</em> spp.</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><em>Neisseria</em> spp.</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><em>Enterobacter</em>, other (e.g., coliforms)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td><em>Enterococcus</em> (<em>S. faecalis</em>, <em>S. faecium</em>)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td><strong>Fungus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Culture negative</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Abbreviations: ESI, exit site infection; P3, Polysporin Triple.

**Secondary analyses**

Results from evaluation of the relationship using time Epochs\(^9\) yielded similar results (data not shown). As noted previously, the management of ESI was highly variable because the study protocol left management of the ESI to the physician’s discretion. No statistical difference was seen between patients receiving systemic or nonsystemic treatment of ESI, although a trend to harm associated was seen with systemic treatment (HR 16.7; 95% CI, 6.4-43.6) compared with nonsystemic treatment (HR, 6.0; 95% CI, 1.4-25.5). Because only one episode of both ESI and peritonitis was seen with the same organism, no further analysis was attempted.

**Discussion**

Our study estimates the hazard of peritonitis, shortly after an ESI is diagnosed, to be six-fold higher than baseline. This has major implications for clinicians involved with PD patients, particularly as ESI management strategies vary highly between physicians and units. We were surprised to find such a high estimated risk associated with ESI, particularly because most ESIs were managed promptly with either topical or systemic therapies. With the current
strategies to detect and treat ESIs promptly, we anticipated that we would see considerably lower risks. In addition to confirming previous reports\textsuperscript{7-27} that patients with an ESI are at increased risk of peritonitis in the immediate post-ESI period, and quantifying this risk, our data showed two additional observations: microbiological inconsistency and lack of effect with aggressive ESI treatments.

Before obtaining the study results, we anticipated that ESIs with Gram-positive organisms or \textit{Pseudomonas} spp. would be highly associated with corresponding bacterial peritonitis infections. We hypothesized that peritonitis would be caused by the same organisms because of contamination of the patient’s hands and equipment when performing exit site care, the presence of catheter biofilm and, to a lesser extent, because of bacterial tracking along the catheter wall. In contrast, we found that the bacterial cultures from the ensuing peritonitis were often different from the organisms causing ESI. We considered three possible explanations for the microbiological inconsistency. First, it is possible that the relationship we observed is purely an artefact of our study design. Because we identified patients at the time of their first ESI after recruitment into the study, it is plausible that we simply identified a high-risk group. Patient-specific factors (hygiene, immunocompetence, psychosocial circumstances, \textit{etc.}) may place some individuals at a higher baseline risk of infection compared with others. These individuals would present earlier with their first infection, and then have a higher incidence of subsequent random infections that would look similar to an increased risk of peritonitis after the first infection. We believe this to be an unlikely explanation because one would then expect little or no change in the estimated risk of peritonitis over time (because these individuals are always at high risk). In contrast, we observed a trend to decreasing risk over time from ESI diagnosis. A second explanation is that it is possible that ESI affects immunomodulatory pathways and is associated with an overall increase in predisposition to bacterial infection, much in the same way that patients with sepsis or influenza are at increased risk of secondary bacterial infections. The dialysis population is already known to be immunocompromised, and we thus thought this may be plausible and searched the literature for similar data. Although we were unable to find any published data relating increased infection associated with tunnelled hemodialysis catheters, or in other immunocompromised nonrenal populations that support bacterial super-infection after mild skin infections, we still believe this to be plausible and suggest further research may be required to evaluate this hypothesis. Last, we questioned if laboratory culture techniques could lead to the observed microbiological inconsistency. Skin swabs would likely be cultured in a lab setting for a specific time or until a positive growth. The samples are unlikely to be cultured for much longer, particularly if the organism grown is consistent with skin infection. Culture plates would be discarded and likely cultures not observed further for alternative slow growing or unusual organisms. Consequently, the treatment used for the skin organism may be appropriately targeted at
the skin organism detected, but not target any other associated organisms. These may then grow and subsequently lead to peritonitis. Although this is an interesting theory, using the data collected as part of this study, we are unable to further comment on whether this may be true or not and again await further research in the field.

In addition to the microbiological inconsistency detailed above, we also found that treatment of the exit site did not reduce the risk of subsequent peritonitis. At the time of the study design, there were no widely available evidence-based protocols for the management of ESIs and the protocol allowed for individualized management of the ESI. The aggressiveness of treatment seemed to vary widely between the five different primary nephrologists who provided regular dialysis care (data not shown). As a result, many cases of ESI were treated with systemic antibiotics (41.1%), whereas others were treated only with topical therapies. We were again intrigued to find a nonstatistical trend to lower rates of peritonitis in those with topical therapies and higher in those who received systemic treatments (defined as oral, intraperitoneal or intravenous antibiotics). Although these data are difficult to interpret because of low numbers of ESI infections, and consequently low power and confounding by indication, they do raise the question of whether systemic therapy is warranted or better.

One of the strengths of this study is that data were collected as part of a blinded multicenter RCT. It is unlikely that biases, arising from missed or undocumented ESI are present. In addition, because of the long prospective follow-up, it is also unlikely that any peritonitis episodes were missed. On the other hand, we have shown wide CIs around the HRs because of a relatively small sample of patients enrolled in our RCT and the low rate of infection. The data, however, still support increased risk in the immediate post-ESI period because, in all cases, the lower CI limits remained substantially >1. It is worth noting that some patients had <60 days follow-up after the ESI start, including 22.7% with <30 days of follow-up after the ESI. This could potentially have led to an underestimation of the extent of the increase in peritonitis risk after ESI. Further extrapolation beyond 60 days was not possible because of the low incidence of ESI. In the context of a RCT, one may arguably see an atypical relationship that arises from the use of an experimental therapy. Our primary results showed that the use of Polysporin Triple was associated with an increase in observed fungal infections; however, because none of the peritonitis events following an ESI were fungal, this is unlikely to have affected the association reported in this manuscript.

In conclusion, we have demonstrated the presence of a strong association between ESI and the development of peritonitis in PD patients. The risk of peritonitis was maximal shortly after the diagnosis of an ESI and decreased over time but remained above baseline even 60 days after the ESI. These data suggest that research is required to assess if strategies to improve the early detection of ESIs may be useful in the prevention of peritonitis and serve to question whether current treatment of ESIs are beneficial.
Acknowledgements
The authors would like to acknowledge Dr. Raymond T. Krediet, MD for his support and valuable advice. This study was funded in part by a grant from the Kidney Foundation of Canada. A.T.N.v.D. received funding from The Dutch Kidney Foundation (Nierstichting Nederland: KSBS 10.0047).
References


Chapter 5

A qualitative systematic review of the literature supporting a causal relationship between exit site infection and subsequent peritonitis in patients with end-stage renal disease treated with peritoneal dialysis

Anouk T.N. van Diepen, Sarbjit V. Jassal

Peritoneal Dialysis International 2013
Volume 33, pages 604-610

Abstract

Objective: The objective of our research was to summarize and review evidence supporting a causal relationship between exit site infection and peritonitis in peritoneal dialysis (PD) patients.

Data Sources: We undertook a qualitative review of studies retrieved from MEDLINE, EMBASE and PubMed, and supplemented that process with hand search of references and abstracts in the literature.

Study Selection: Our quality criteria were based on the Paediatric Risk of Mortality guidelines, definitions, and recommendations from the International Society of Peritoneal Dialysis (ISPD), and the Bradford Hill criteria for causality. All identified abstracts were reviewed for content. Of 776 abstracts, 59 were selected for full-text evaluation, and 22 of those met the ISPD criteria for good-quality research in PD-related infections. Of the 22 eligible studies, 9 met the study’s quality criteria and were included in the summative analysis. No articles reported sufficient data for a quantitative analysis.

Data Extraction: Information on study design, study population characteristics, definitions, peritonitis rates, exit-site care protocol, exit-site treatment protocol, follow-up period, potential bias, and outcomes was extracted. Criteria for including data in the final study were determined using the ISPD guidelines.

Data Synthesis: Of the 9 included studies, 8 suggested that a history of exit site infection increased the risk for subsequent peritonitis. Of those studies, 3 met 5 causality criteria, 4 met 4 causality criteria, and 1 met 3 causality criteria.

Conclusions: The literature provides weak evidence to support a causal relationship between exit site infection and subsequent peritonitis. Few criteria for causation were met. We were unable to attribute causation and could assume an association only. The exclusion of studies focusing on PD-related tunnel infections may be viewed as both a strength and a limitation of the present work.
Qualitative review: association between ESI and peritonitis

Introduction

Catheter related infections are the most common, and serious, of all complications associated with chronic peritoneal dialysis (PD). Although infection rates have declined in recent years, bacterial and fungal infections continue to be the leading cause of technique failure and mortality in PD patients.1-7 It has long been assumed that a bacterial (or fungal) infection around the exit site (“exit site infection” (ESI)) will lead to tracking along the catheter path and predispose to peritonitis. As a result, the International Society for Peritoneal Dialysis (ISPD) and other leading authorities have recommended measures to help prevent, detect, and aggressively treat ESIs.3-7 We questioned whether the literature supports only a clinical association between ESI and peritonitis or whether the data are sufficient to establish causality. The distinction is important to those interested in developing novel or innovative strategies to reduce the incidence of peritonitis, particularly if aggressive strategies to reduce or manage ESIs inadvertently increase the risk of peritonitis by an alternative mechanism.

In the present study, we used robust epidemiologic criteria (Bradford Hill criteria) to make a distinction between causation and association.8 The Bradford Hill criteria outline the conditions that should ideally be fulfilled to establish a causal relationship between two events. In the absence of those criteria, an association only and not causality must be assumed.

Association and causation are epidemiological concepts. The term “association” describes any relationship between two or more variables without attributing cause and effect. Such variables might be associated indirectly through other important characteristics of the patient or the environment. In contrast, the term “causation” implies that changes in (or exposure to) variable A directly caused changes in variable B. In medicine, causation can rarely be proven; however, certain characteristics can be sought to support causality.

The objective of the present study was to systematically review the literature and summarize the evidence supporting a causal relationship between ESI and peritonitis.

Methodology

We used a 3-step process: literature search, data quality assessment, and data extraction.

Literature search and eligibility criteria

We undertook a literature search with the help of a specialist librarian. Three medical databases (MEDLINE, EMBASE, PubMed) were systematically searched, and relevant reference lists and published abstracts were subsequently hand-searched (Figure 1). Search
terms used included “Peritoneal Dialysis” AND “Peritonitis” AND 1 of 3 terms associated with ESIs ("Catheter-related infections" OR "Catheterization/ae" OR “(exit site adj4 infection*). mp"). Determination of tunnel infections was felt to be highly dependent on both screening and diagnostic protocols within units, and therefore “tunnel infection” was not included as a search term. All identified abstracts were screened, and selected full texts were reviewed to ensure that they met the eligibility criteria: inclusion of information about ESIs and peritonitis, and specificity to peritoneal dialysis patients.

Figure 1. Literature Search
Data quality assessment
Eligible studies underwent quality assessment using criteria specific to our question. The criteria were developed in two steps. In the first step we used the ISPD definitions of good-quality research on PD-related infections (Table 1) to determine criteria for “adequate quality”.

We then identified which question-specific data elements were required to fulfill each of the 9 Bradford Hill criteria for causation.

Table 1. Variables for quality assessment of the literature reporting a relationship between ESI and peritonitis

<table>
<thead>
<tr>
<th>Manuscript should include the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Baseline characteristics:</td>
</tr>
<tr>
<td>- Study design (e.g. prospective, retrospective)</td>
</tr>
<tr>
<td>- Study population inclusion and exclusion criteria</td>
</tr>
<tr>
<td>- Population age, gender, race, percentage of diabetic patients</td>
</tr>
<tr>
<td>- Follow-up duration (to include follow-up period and methodology of collecting information)</td>
</tr>
<tr>
<td>• Clear definitions of both exit site infection and peritonitis that were consistent with ISPD guideline recommendations.</td>
</tr>
<tr>
<td>• Clear definitions of both recurrent and relapsing peritonitis that were consistent with contemporary ISPD guideline recommendations.</td>
</tr>
<tr>
<td>• Sufficient data to calculate peritonitis rates as episodes/patient/year (overall and/or for individual organisms) or the use of time to peritonitis.</td>
</tr>
<tr>
<td>• Clear description of the exit site care protocol (e.g. use of prophylaxis, eligible recipients).</td>
</tr>
<tr>
<td>• Clear description of the treatment of exit site infection (e.g. was it protocol-based or left to the physicians discretion).</td>
</tr>
</tbody>
</table>

Abbreviations: ISPD, International Society for Peritoneal Dialysis.

Data Extraction
In the final step, demographic data, publication data, and risk results were all extracted using a systematic approach. All data were extracted by a single observer (ATNVD).

Results

Identification of qualitative evidence
The literature search revealed a total of 776 papers. Reference lists were hand-searched and an additional 9 papers identified. We excluded 726 papers because they did not report data pertaining to both ESIs and peritonitis rates. Papers focussing solely on tunnel infections or nasal carriage were excluded. We assessed the full texts of the remaining 59 articles for eligibility. After assessment, an additional 37 papers were excluded because they did not contain information relevant to the relationship between ESIs and peritonitis. Table 1 sets out our criteria for adequate quality. Those criteria were applied to all 22 papers that reported relevant information. Among those 22 papers, only 9 met sufficient criteria to be included in the final analysis (Figure 1, Table 2).
Table 2. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Nr. Of Patients</th>
<th>Age in years</th>
<th>Follow-up per patient</th>
<th>Country</th>
<th>Definition ESI-related peritonitis</th>
<th>Reported relationship</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piraino et al. 1986&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Prospective</td>
<td>137</td>
<td>50 ± 15 (19-81)</td>
<td>15.0 ± 9.6 months (3-46 months)</td>
<td>U.S.A.</td>
<td>N/A</td>
<td>Yes</td>
<td>1.42</td>
</tr>
<tr>
<td>Piraino et al. 1987&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Prospective</td>
<td>137</td>
<td>50 ± 15 (19-81)</td>
<td>15.0 ± 9.6 months (3-46 months)</td>
<td>U.S.A.</td>
<td>≤2 weeks</td>
<td>Yes</td>
<td>1.42</td>
</tr>
<tr>
<td>Lee et al. 1992&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Prospective</td>
<td>130</td>
<td>51 ± 13 (7-77)</td>
<td>Maximum 1 year</td>
<td>Singapore</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Gupta et al. 1996&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Partly Prospective</td>
<td>512</td>
<td>48 ± 15 (35-65)</td>
<td>From ESI or peritonitis to catheter removal</td>
<td>U.S.A.</td>
<td>≤2 weeks</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Paquay et al. 1996&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Partly Prospective</td>
<td>118</td>
<td>43 (17-84)</td>
<td>17 months (2 days-73 months)</td>
<td>Holland</td>
<td>N/A</td>
<td>Yes</td>
<td>1.54</td>
</tr>
<tr>
<td>Crabtree et al. 1999&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Prospective</td>
<td>57</td>
<td>49.6 (15-78)</td>
<td>From catheter implant to max. end of study</td>
<td>U.S.A.</td>
<td>≤4 weeks</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Szeto et al. 2007&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>152</td>
<td>52.3 ± 13.5</td>
<td>From peritonitis to at least 3 months after completion antibiotics</td>
<td>China</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
</tr>
<tr>
<td>Lobo et al. 2010&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>330</td>
<td>53 ± 19</td>
<td>At least 20 days to max. end of study</td>
<td>Brazil</td>
<td>N/A</td>
<td>Yes</td>
<td>2.6</td>
</tr>
<tr>
<td>Van Diepen et al. 2012&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Prospective</td>
<td>203</td>
<td>60 ± 14 (23-100)</td>
<td>18 months (0.1-18.0 months)</td>
<td>Canada</td>
<td>≤30 days</td>
<td>Yes</td>
<td>6.32</td>
</tr>
</tbody>
</table>

Abbreviations: N/A, data not available; ESI, exit site infection.
Study characteristics
Table 2 summarizes the baseline characteristics of the 9 studies. Although all the studies reported peritonitis rates (range: 0.38-1.36 episodes per patient-year), only 5 of the 9 studies\cite{19-23} met the reporting standards recommended by the ISPD guidelines.\textsuperscript{5} The incidence of exit site infections varied broadly between studies, with an overall trend to declining rates over time: studies published before 1990 reported 1.02 episodes per patient-year,\textsuperscript{15,16} and studies from subsequent years reported 0.20-0.80 episodes per patient-year.\textsuperscript{17-23}

Bradford Hill criteria for causation
Of the 9 studies that met our criteria for a full qualitative review,\textsuperscript{15-23} eight\textsuperscript{15-17,19-23} reported a relationship between ESI and peritonitis, and 1 study\textsuperscript{18} reported no relationship between ESI and recurrent and relapsing peritonitis. Table 3 shows the results of the quality assessment. The criterion of biological feasibility was considered fulfilled because it is widely accepted that organisms can track along implanted devices. In PD patients, the organisms would track along the catheter wall between the exit site and the peritoneum. Clear evidence of a temporal relationship was missing in 3 reports\textsuperscript{16,18,22} that did not have a clear definition of ESI-related peritonitis. In those 3 studies, it was unclear whether peritonitis preceded, occurred simultaneously with, or presented after ESI. Sufficient data were given in 5 studies\textsuperscript{15-17,21,23} to allow for derivation of the relative risk ratio of peritonitis after ESI compared with peritonitis without ESI (range: 1.4-6.3). Other studies\textsuperscript{18-20,22} did not include sufficient data for a calculation of a risk ratio from their results.

Only 1 study reported whether an individual’s hazard of peritonitis declined over time.\textsuperscript{23} Causation criteria suggest that other possible explanations for the identified relationship should be sought and, to establish causality, excluded. Of the studies reviewed, seven\textsuperscript{15,17-19,21-23} discussed other explanations for the relationship, but were unable to support or refute the relative importance of those explanations. The study by Lee et al.\textsuperscript{20} controlled for the overrepresentation of patients with diabetes in their population. Only 1 study\textsuperscript{16} did not discuss any alternate conclusions.
Table 3. Quality assessment based on the principles of the Bradford Hill criteria for causation

<table>
<thead>
<tr>
<th></th>
<th>References that fulfilled criterion</th>
<th>References that did not fulfill criterion</th>
<th>References without available data</th>
<th>Total number of references that fulfilled criteria</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporality</td>
<td>23</td>
<td>16,19,22</td>
<td>15,17,18,20,21</td>
<td>1</td>
<td>Literature did not report on the temporal relationship between ESI and peritonitis</td>
</tr>
<tr>
<td>Strength</td>
<td>15-17,21,23</td>
<td>--</td>
<td>18-20,22</td>
<td>5</td>
<td>Only some literature supported the identified relationship between ESI and peritonitis with a risk ratio</td>
</tr>
<tr>
<td>Biological gradient</td>
<td>--</td>
<td>--</td>
<td>15-23</td>
<td>0</td>
<td>Data was unavailable to determine the gradual biological influence of ESI leading to an increased incidence of peritonitis</td>
</tr>
<tr>
<td>Analogy</td>
<td>20</td>
<td>15,17-19,21-23</td>
<td>16</td>
<td>1</td>
<td>Most literature concerning the relationship between ESI and peritonitis was unable to refute other explanations for the reported relationship</td>
</tr>
<tr>
<td>Experiment</td>
<td>17,22</td>
<td>--</td>
<td>15,16,18-21,23</td>
<td>2</td>
<td>Literature reporting an intervention during follow-up showed a reduction of ESI, which led to a reduction in the incidence of peritonitis</td>
</tr>
<tr>
<td>Biological plausibility</td>
<td>15-23</td>
<td>--</td>
<td>--</td>
<td>9</td>
<td>Literature supports an ESI to be biologically plausible to lead to peritonitis</td>
</tr>
<tr>
<td>Specificity</td>
<td>--</td>
<td>15-23</td>
<td>--</td>
<td>0</td>
<td>Literature was unable to eliminate confounding factors with effect on the relationship between ESI and peritonitis</td>
</tr>
<tr>
<td>Consistency</td>
<td>15-17,19-23</td>
<td>18</td>
<td>--</td>
<td>8</td>
<td>The relationship between ESI and peritonitis was seen in different study populations and settings worldwide</td>
</tr>
<tr>
<td>Coherence</td>
<td>15-23</td>
<td>--</td>
<td>--</td>
<td>9</td>
<td>Literature supports the relationship between ESI and peritonitis is compatible with current clinical knowledge and existing theory</td>
</tr>
</tbody>
</table>

Abbreviations: ESI, exit site infection.
Any intervention that has an impact on one variable and effect a change in another (for example, a treatment that reduces the incidence of ESI that reduces peritonitis) can support a determination of causality between ESI and subsequent peritonitis. In 2 studies, an intervention may have affected the ESI incidence. In one of those studies, the authors reported results before and after the introduction of the Y-set in combination with an intensified antibiotic treatment protocol for ESI; in the other, the exit site prophylaxis protocols were changed. Both studies showed a decline in both the ESI rate and the peritonitis rate, suggesting causality. (Ideally an attempt would have been made to withdraw therapy and see a return to baseline infection rates, but taking that action was not feasible). Overall, the literature was consistent across the various study populations and study settings. Because 4 studies did not report the strength of the observed association, consistency across the estimated risk was not established. Nor was it possible to comment on the presence or absence of a biological gradient (akin to dose-response) by searching for a graduated risk in either the number of ESIs or the risk attribution.

**Discussion**

We used the Bradford Hill criteria for causation to evaluate whether the literature was able to establish causality between ESI and subsequent peritonitis. According to our strict qualitative review, the data supported an association, but were insufficient to demonstrate a causal relationship. The presence of an association questions (a) whether the relationship depends on the individual (a patient with an ESI has an inherent immunological risk, placing him or her at higher risk of peritonitis) or (b) whether the ESI itself directly compromises the patient and predisposes the individual to a newly increased risk of peritonitis. We believe that the answer is important because it can inform the development of novel strategies to reduce peritonitis. If the answer is (a), then novel strategies will target identification of the patient at risk and apply patient-level interventions; if the answer is (b), novel treatments will target ESI prevention.

We were surprised to find that the literature did not establish a causal relationship between ESI and subsequent peritonitis. We suggest that further work is required in the field. We recommend the wider adoption of the recent ISPD guidelines for research into infections and the strict inclusion of a time interval in papers reporting an association between ESI and any related peritonitis episodes. Published articles should include a clear definition of ESI-related peritonitis, support the results with a numeric estimate of the risk strength, and distinguish between ESI and tunnel infection if possible. We also raise the question of whether, as PD physicians, we need to reconsider the correctness of the assumption that ESI leads directly to subsequent peritonitis and to investigate phenotype in patients in whom
ESI leads to subsequent peritonitis. Researchers might then be able to identify the nature of important contributing factors.

**Acknowledgements**

The authors would like to acknowledge Raymond T. Krediet, MD, for his support and valuable advice. Anouk T.N. van Diepen received funding from The Dutch Kidney Foundation (Nierstichting Nederland: KSBS 10.0047).

**Disclosures**

In the past three years, SVJ has received speaker honoraria from Amgen Canada.
Qualitative review: association between ESI and peritonitis

References


Chapter 6

The association between glucose exposure and the risk of peritonitis in peritoneal dialysis patients

Anouk T.N. van Diepen, Sadie van Esch, Dirk G. Struijk, Raymond T. Krediet

Submitted for publication
Abstract

Background and objective: Little or no clinical evidence is available on the association between glucose exposure and peritoneal host defense in peritoneal dialysis (PD) patients. The objective of the present study was to quantify the exposure to glucose during the first year on PD and investigate the association with subsequent peritonitis.

Design, setting, participants and measurements: We analyzed prospectively collected demographic and peritonitis data from incident adult PD patients between 1990 and 2010. For the present study, we conducted a review of both in- and outpatient medical records of all patients to obtain their day-to-day dialysis schemes during the first year on peritoneal dialysis. From these data, the average exposure to glucose was quantified. The exposure was stratified into a low and high glucose group based on the median, analyzed per standard deviation and in quartiles. Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals for the association between glucose exposure and peritonitis. Adjustments were made for age, sex, primary kidney disease, diabetes mellitus, Davies comorbidity score and the treatment period.

Results: In total 230 patients were included in the study of whom 151 (66%) experienced a first peritonitis episode. The median follow-up time was 2.6 years (IQR: 1.9-3.8) in the low glucose group and 3.1 (IQR: 2.1-4.2) in the high glucose group. After adjustment for confounding factors, high glucose exposure was associated with a 19% lower risk of peritonitis compared with low glucose exposure with a wide confidence interval (HR: 0.81; 0.55-1.17). No association was present when glucose exposure was analysed per SD (HR: 0.98; 0.79-1.21) or patient quartiles were applied.

Conclusions: Exposure to glucose is not associated with an increased risk of peritonitis. The equilibrium between glycemic harm to peritoneal host defense and detrimental effects of glucose on invading microorganisms may determine the susceptibility to peritoneal infection.
Introduction

Long-term exposure to dialysis solutions causes structural changes to the peritoneum in peritoneal dialysis (PD) patients. The unphysiological composition of the dialysate has been hypothesized to compromise peritoneal host defense. Many in vitro, ex vivo and animal studies have been performed to investigate this hypothesis. These studies point to the detrimental effects of acidic pH, glucose, hyperosmolality, lactate buffer and GDPs on monocytes, peritoneal macrophages, neutrophils and mesothelial cells. However, the majority of these studies cannot be translated to the clinical situation due to a lack of follow-up, non-realistic exposure levels or the absence of renal failure. Over the last decade, multiple randomized controlled trials have been performed to compare the incidence of peritonitis between patients randomized to a high or low GDP regimen and, when meta-analyzed, found no difference. Bicarbonate buffering reduced the length of time to peritonitis in a randomized controlled trial (RCT), but these results still need to be confirmed in other populations. Indirectly, RCTs that compared icodextrin with glucose for the long-dwell, investigated a glucose sparing to a non-glucose sparing regimen reported no difference in peritonitis episodes between the two arms. Therefore the composition of the dialysate appears to be harmful in non-clinical experiments, but clinical studies demonstrate otherwise.

None of the clinical studies that investigated glucose exposure and the incidence of peritonitis quantified the exposure to glucose and assessed a dose-response relationship. Furthermore, the literature concerning quantification of glucose exposure used calculations that can only be applied to continuous ambulatory PD (CAPD) patients and provide very rough estimates of the actual glucose exposure. Therefore, it is unknown whether the estimated glucose exposure is associated with an increased susceptibility to peritonitis in patients. The objective of the present study was to quantify the exposure to glucose during the first year on PD and to investigate the association with subsequent peritonitis. Our hypothesis was that exposure to higher concentrations of glucose is associated with an increased risk of peritonitis and a shorter time to the first peritonitis episode.

Materials and Methods

Study design

The present study was conducted in a large prospective database of incident PD patients, aged >18 years, receiving dialysis in a Dutch tertiary-care university hospital between January 1990 and July 2010. All patients were treated with solutions obtained from Baxter Healthcare S.A. (Castlebar, Ireland). Data on baseline demographics and peritonitis episodes...
was collected prospectively in the database as part of routine clinical care. For the present study, we conducted a review of both in- and outpatient medical records of all patients to obtain their prescribed day-to-day dialysis schemes during the first year on dialysis. Patients who remained less than one year on PD were excluded, because we could not obtain complete information about glucose exposure during their first year on PD. Patients with peritonitis during the first year on PD were excluded to avoid an effect of peritonitis on exposure. Time of follow-up was defined as the number of days between the first 365 days on PD and the date of censoring.

Demographic data collection
Routinely collected demographic data at the start of PD included dialysis modality (CAPD/APD), age, sex, and primary kidney disease. Additional data collected during the review of medical records included diabetes mellitus, Davies comorbidity score,\textsuperscript{24} the use of an angiotensin-converting-enzyme inhibitor (ACE) and the use of an angiotensin II receptor blocker (ARB). Because no data on 24-hour urine urea and creatinine was available, we used serum beta-2-microglobulin to estimate residual renal function. It is known from literature that this parameter can be used to estimate residual glomerular filtration rate.\textsuperscript{25}

Glucose exposure
Day-to-day dialysis schemes were retrospectively collected in a large database. Those between 0 and 180 days on PD were neglected because this is a period, in which the PD scheme is often not stable, due to adjustments that are required by the patients’ transport status and hydration state. On a day without information on the dialysis scheme it was assumed that the scheme of the previous day was followed. Data collected about the dialysis schemes of CAPD patients included the number of dwells per day, dwell volume, glucose concentration, the dwell time and the type of dialysis solution. Data collected for automated PD (APD) patients included the total treatment volume, total treatment time, number of cycles, tidal percentage, dwell volume and glucose concentration per cycle, and dwell volume and glucose concentration of the last bag. From these data, the average exposure to glucose during 24 hours between 180 and 365 days can be quantified. Three assumptions were made for the quantification of the glucose exposure: 1) Glucose absorption from the peritoneal cavity averages 60% after 4 hours\textsuperscript{26} 2) glucose absorption follows first order kinetics, which means that it becomes linear after logarithmic transformation 3) the geometric mean of glucose exposure in the middle of the dwell is the closest approximation of the average glucose exposure during the total dwell. The following calculation can be made for the geometric mean glucose concentration of a 4 hr dwell: $\ln G_m = \ln(G_i) + (\ln(0.4G_i) - \ln(G_i))/2$. In this equation $\ln G_m$ is the natural logarithm of the geometric mean glucose concentration, $G_i$ is the initial glucose dialysate glucose concentration and 0.4 indicates that after 4 hours only 40% of the
Glucose exposure and peritonitis risk

initial glucose concentration is present. The initial glucose concentration for 1.36% glucose is 70 mmol/L, for 2.27% glucose 118 mmol/L and for 3.86% glucose 198 mmol/L. Calculation of $G_m$ for any dwell time can be done using $e^{\ln G_m}$. The average glucose exposure during 24 hours is the sum of all $G_m$ values of each dwell multiplied by the fractional duration of the dwell per 24 hours. Examples are given in appendix 1 (see appendix 3 in chapter 10 of this thesis).

Statistical analyses

Baseline characteristics were stratified according to the median of the glucose exposure. Continuous data are expressed as mean values and standard deviations (SD) or median and interquartile ranges (IQR) as appropriate and categorical variables in proportions. Differences between baseline characteristics were tested with an unpaired Student’s t-test, Mann-Whitney (continuous data) or chi-square test (categorical data). Unadjusted cumulative survival curves over a period of five years according to high and low glucose were calculated, with the first peritonitis episode, death, switch to HD and transplantation as the events.

Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals for the association between glucose exposure and peritonitis. For these analyses, glucose exposure was stratified into high or low exposure based on the median, assessed per standard deviation (SD) and in quartiles. Adjustments were made for age, sex, primary kidney disease, diabetes mellitus, Davies comorbidity score and the treatment period (1990-1996 (Dianeal® only), 1997-2004 (transition period and introduction of icodextrin), 2005-2010 (Physioneal® only)). Additional Cox proportional hazard models were used to calculate crude and adjusted hazard ratios (HRs) and 95% confidence intervals for the association between glucose exposure and severe, *Staphylococcus aureus* or long-lasting peritonitis. For these analyses, glucose exposure was stratified into high or low exposure. Severe peritonitis was defined as a leukocyte count >1,090 cells/mm³ on day 3 or >100 cells/mm³ on day 5 of the peritonitis episode and compared with patients without severe peritonitis. Causative microorganisms were dichotomized in *Staphylococcus aureus* and compared with patients who did not suffer from *Staphylococcus aureus* peritonitis. The duration of the peritonitis episode was calculation and dichotomized in long duration (> 14 days) and compared with patients who did not experience a first peritonitis episode that lasted longer than 14 days. All data analyses were performed using SPSS 20.0 and STATA 12.1.

Sensitivity analyses

The influence of CAPD/APD on peritonitis risk is uncertain and therefore its role as a confounder. A sensitivity analysis, modality (CAPD/APD) at the start of dialysis was added to
the fully adjusted model to explore its influence on the association. Residual renal function at the start of dialysis might be a confounder of the association. However, this information was available in a limited number of patients (n=99). Therefore residual renal function according to serum b2-microglobulin was added to the model in a sensitivity analysis to examine its impact on the association.

Results

Population characteristics
Medical records of 479 incident patients starting PD treatment between January 1990 and July 2010 in our center were reviewed. After excluding patients with incomplete or lost files (n=39) or less than one year until peritonitis or censoring (n=210) a total of 230 patients could be included. The baseline characteristics of the study population are summarized in Table 1. The median and mean of the glucose exposure between six and twelve months was 44 mmol/L during 24 hours with a SD of 18. Patients with a higher glucose exposure were more often treated with CAPD and had lower residual renal function. The median follow-up time was 2.6 years (IQR: 1.9-3.8) in the low glucose group and 3.1 (IQR: 2.1-4.2) in the high glucose group. Of all patients, 147 (64%) experienced a first peritonitis episode, of which 77 were treated with low glucose exposure and 70 with high glucose exposure. The main reasons for censoring in patients without peritonitis were death (low glucose: 14%; high glucose: 16%) and transplantation (low glucose: 13%; high glucose: 11%) (Figure 1).

Glucose exposure and peritonitis
Figure 1 shows the unadjusted cumulative incidence survival curves. No difference in the crude peritonitis free survival was observed between the patients exposed to high and low glucose. Table 2 shows crude and adjusted hazard ratios (HRs) and 95% confidence intervals for high vs. low glucose exposure, per glucose SD and in patient quartiles. The unadjusted HRs demonstrated a consistent trend that is suggestive of a protective association between higher glucose exposure and peritonitis. However, when adjustments for confounding factors were made, the trend towards an association lost statistical significance. High glucose exposure remained associated with a 19% lower risk of peritonitis compared with low glucose exposure, but the confidence interval was fairly wide and could indicate both a 45% decreased risk and a 17% increased risk of peritonitis in the high exposure group. Also, no association was present when glucose exposure was evaluated per SD or when patient quartiles were applied.
Table 1: Baseline demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>'Low exposure' Glucose exposure &lt;44 mmol/L/ during 24h</th>
<th>'High exposure' Glucose exposure ≥ 44 mmol/L/ during 24h</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr. of patients (%)</td>
<td>115</td>
<td>115</td>
<td></td>
</tr>
<tr>
<td>Age (median (IQR))</td>
<td>54 (42-67)</td>
<td>57 (44-66)</td>
<td>0.93</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>64</td>
<td>58.</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>29</td>
<td>33</td>
<td>0.48</td>
</tr>
<tr>
<td>Primary kidney disease (%)</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>24</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>18</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>20</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>37</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Davies comorbidity score (%)</td>
<td>9</td>
<td>8</td>
<td>0.85</td>
</tr>
<tr>
<td>Dialysis modality (%)</td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>CAPD only</td>
<td>41</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>APD only</td>
<td>23</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>CAPD switched to APD</td>
<td>33</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>APD switched to CAPD</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ACE/ARB usage (%)</td>
<td></td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>ARB only</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ACE only</td>
<td>46</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>ACE + ARB</td>
<td>12</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Serum β-2 microglobulin (mg/L)*</td>
<td>19.9 ± 7.0</td>
<td>23.4 ± 8.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose exposure (mmol/L/24h; median (IQR))</td>
<td>27 (21-33)</td>
<td>51 (46-61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time on PD (years; median (IQR))</td>
<td>2.6 (1.9-3.8)</td>
<td>3.1 (2.1-4.2)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; CAPD, Continuous ambulatory peritoneal dialysis; APD, Automated peritoneal dialysis; ACE, Angiotensin I converting enzyme inhibitor; ARB, angiotensin II receptor blocker; *at baseline and available in a limited number of patients (n=99).

Figure 1: Unadjusted cumulative incidence survival curves for peritonitis-free survival, peritonitis, switch to HD, transplantation and death on PD for patients exposed to low and high glucose exposure.
Table 2. crude and adjusted HRs (95% CI) associated with glucose exposure during 6-12 months on peritoneal dialysis

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI) glucose high vs. glucose low</th>
<th>HR (95% CI) per SD glucose</th>
<th>Qrt1: 0-27.0 mmol/L during 24h</th>
<th>Qrt2: 27.1-41.0 mmol/L during 24h</th>
<th>Qrt3: 41.1-51.4 mmol/L during 24h</th>
<th>Qrt4: 51.5-86.5 mmol/L during 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>0.71 (0.51-0.99)</td>
<td>0.88 (0.74-1.05)</td>
<td>1.00</td>
<td>0.80 (0.50-1.28)</td>
<td>0.74 (0.46-1.18)</td>
<td>0.79 (0.50-1.26)</td>
</tr>
<tr>
<td>Adjusted model 1</td>
<td>0.72 (0.51-1.01)</td>
<td>0.90 (0.75-1.07)</td>
<td>1.00</td>
<td>0.77 (0.48-1.24)</td>
<td>0.76 (0.47-1.21)</td>
<td>0.82 (0.51-1.32)</td>
</tr>
<tr>
<td>Adjusted model 2</td>
<td>0.74 (0.53-1.03)</td>
<td>0.90 (0.76-1.07)</td>
<td>1.00</td>
<td>0.74 (0.46-1.19)</td>
<td>0.77 (0.48-1.24)</td>
<td>0.77 (0.48-1.24)</td>
</tr>
<tr>
<td>Adjusted model 3</td>
<td>0.81 (0.55-1.17)</td>
<td>0.98 (0.79-1.21)</td>
<td>1.00</td>
<td>0.88 (0.52-1.50)</td>
<td>0.97 (0.55-1.72)</td>
<td>0.97 (0.53-1.77)</td>
</tr>
</tbody>
</table>

Abbreviations: HR, Hazard ratio; SD, standard deviation; Qrt, quartile; Adjusted model 1: age, sex, primary kidney disease; Adjusted model 2: + DM and Davies score; Adjusted model 3: + Period effect.
Glucose exposure and peritonitis risk

Severity, causative microorganism and duration of the peritonitis episode
Of all first peritonitis episodes, 49% (n=74) lasted longer than 14 days, 17% (n=26) could be qualified as a severe peritonitis episode and in 6% (n=9) of the cases Staphylococcus aureus was the causative microorganism. Unadjusted HRs were suggestive of an association between high glucose exposure and decreased risk of severe peritonitis (HR: 0.71; 95% CI: 0.46-1.10), Staphylococcus aureus peritonitis (0.83; 0.40-1.72) or a peritonitis episode that lasts more than 14 days (0.71; 0.55-0.91). The low event rate of severe and Staphylococcus aureus peritonitis made further adjustments impossible. However, when adjustments were made, high glucose exposure might lead to a 14% decreased risk of a peritonitis episode that lasted more than 14 days, but the confidence interval was fairly wide (0.86; 0.63-1.17).

Sensitivity analyses
When dialysis modality (CAPD/APD) at the start of dialysis was added to the model, the HRs attenuated (high vs. low HR: 0.84; 0.57-1.23; per SD HR: 1.01; 0.81-1.25). When residual renal function was added to the model, the association became stronger (high vs. low HR: 0.52; 0.26-1.02; per SD HR: 0.71; 0.48-1.05).

Discussion
We demonstrated a novel method for the quantification of glucose exposure that can be used in both CAPD and APD patients. The results of the present study show that glucose exposure during the first year on PD is not associated with the time to subsequent peritonitis. In addition, no association between the amount of glucose exposure and severe peritonitis, Staphylococcus aureus peritonitis or a peritonitis episode that lasts more than 14 days was identified.

Our results are in line with the results from previous RCTs that compared peritonitis risk in patients treated with a glucose sparing to a non-glucose sparing regimen. They are, however, in contrast with a large body of evidence from in vitro, ex vivo and in vivo studies. Two possible explanations for this phenomenon are presented. First, it might be that the experiments were unable to mimic the situation in PD patients. Experimental models often suffered from lack of follow-up, non-realistic exposure levels or the absence of renal failure, which makes translation to clinical practice impossible. A second explanation might be that glucose does not only exert detrimental effects on the peritoneal host defense but also on the invading microorganisms. It could well be that the risk of peritonitis is determined by the balance between harm to the peritoneal host defense on one hand and bactericidal effects on the other hand.
Little is known about the glucose concentrations that are necessary to facilitate bactericidal activity in humans. In vitro studies investigated different honeys and honey-equivalent sugar solutions. Among other components, the high sugar concentration and its osmolality and methylglyoxal (MGO) were identified to be responsible for the bactericidal properties of these honey substances. When we compare the sugar concentrations that were found to facilitate bacterial killing in these in vitro experiments to the glucose concentration in a PD solution, the bactericidal sugar concentrations were much higher than the maximum glucose concentrations in dialysis solutions: about 20% vs. 3.86%/4.25%. Furthermore, the osmolality that was bactericidal in vitro was approximately twice as high as the osmolality of a 3.86% dialysis solution: ± 1000 mOsmol/L vs. 483 mOsmol/L. However, the in vitro bactericidal concentration and osmolality might not be comparable to the exposure necessary to cause intraperitoneal bactericidal or bacteriostatic effects. In patients, randomized controlled trials assessed the effect of topical application of honey for prevention of infections and improved wound healing. It is, however, impossible to extract an effective dosage from these studies and make a comparison to glucose in the dialysis solutions.

The antibacterial properties of MGO were discovered due to its high concentrations in Manuka honey. More interestingly, MGO is one of the glucose degradation products in Dianeal®, Physioneal® and icodextrin as well as in other commercially available dialysis solutions. The concentrations of MGO are 0.5-1 μmol/L in Physioneal®, 4-7 μmol/L in Dianeal® and 2 μmol/L in icodextrin, suggesting that Dianeal® has the highest bacteriostatic capacity. This hypothesis is supported by a previous report by Verbrugh et al. which showed that Dianeal®, amongst other commercially available solutions, did not support survival of Staphylococcus aureus and Staphylococcus Epidermidis in vitro. In our dialysis unit, patients were treated with Dianeal® between 1990 and 1997, with Dianeal® or Physioneal® between 1998 and 2004, and with Physioneal® between 2005 and 2010. The use of icodextrin started in 1997. In our study, patients with higher glucose concentrations were more often treated with Dianeal, whereas patients with lower glucose exposure were more often treated with Physioneal® and icodextrin. Therefore, our results might be influenced by a correlation between higher glucose exposure and higher MGO concentrations in our patients. This could explain the tendency of the estimates towards a protective effect of glucose exposure with respect to peritonitis risk. On the other hand, the MGO concentration differences are small and studies that compared conventional and biocompatible solutions, found no difference in peritonitis risk in a meta-analysis.

To the best of our knowledge, we are the first to study the association between glucose exposure and the severe peritonitis, Staphylococcus aureus peritonitis and peritonitis that lasted more than 14 days. The low event rate of severe and Staphylococcus aureus peritonitis limited our analyses and, although the estimates yielded into the direction of a protective effect of glucose, no association could be attributed. Higher glucose concentrations appeared
to decrease the risk of a peritonitis episode that lasted longer than 14 days but this was not statistically significant.

The present study has several strengths and weaknesses. Although demographic and clinical data and information about peritonitis episodes were collected prospectively, we retrospectively collected day-to-day dialysis schemes during the first year on PD. However, we are confident that a thorough review of complete original medical records was performed. Because data collection was limited to the first year on PD, we are unable to draw conclusions about the influence of glucose exposure beyond the first year on PD.

A major strength of our study is the inclusion of incident PD patients with a long-term follow-up. In addition, a novel method was used to quantify the exposure to glucose. The major advantage of this method is that it can be used for both CAPD and APD patients. Three underlying assumptions supported the calculations. First, Krediet et al. found that glucose absorption was approximately 60% after a 4-hour dwell. In addition, Smit et al. showed that this was not different when dialysis solutions with different glucose concentrations were used or when patients suffered from diabetes. Second, the assumption that glucose absorption during a PD dwell follows first order kinetics has previously been established. Consequently, we assumed that the geometric mean of glucose exposure in the middle of the dwell is the closest approximation of the average glucose exposure during the total dwell.

In conclusion, our study demonstrated no association between glucose exposure during the first year on PD and the subsequent time to peritonitis. This is in line with previous studies in patients. However, an overall tendency towards a protective effect of higher glucose concentrations was observed, although this was not significant in the majority of the analyses. It could well be that the risk of peritonitis is determined by the balance between the harm of dialysis solutions to peritoneal host defense on one hand and their bactericidal effects on the other hand. Future studies should determine whether bactericidal properties of PD solutions might have a clinically relevant function in the prevention of peritonitis.

**Disclosures**

A.T.N. van Diepen was supported by a grant: 12CECPDEU1002, awarded by Baxter Healthcare. Baxter Healthcare was not involved in the collection, interpretation and analysis of the data, or in the decision for writing and submitting this report for publication.
References


Chapter 6


42. Schalkwijk CG, ter Wee PM, Teerlink T: Reduced 1,2-dicarbonyl compounds in bicarbonate/lactate-buffered peritoneal dialysis (PD) fluids and PD fluids based on glucose polymers or amino acids. *Perit Dial Int* 20: 796-798, 2000.


Chapter 7

The first peritonitis episode alters the natural course of peritoneal transport in peritoneal dialysis patients

Anouk T.N. van Diepen*, Sadie van Esch*, Dirk G. Struijk, Raymond T. Krediet
*These authors contributed equally to the manuscript

Peritoneal Dialysis International 2014, in press
doi: 10.3747/pdi.2014.00277
Abstract

**Objective:** Little or no evidence is available on the impact of the first peritonitis episode on peritoneal transport characteristics. The objective of this study was to investigate the importance of the very first peritonitis episode and distinguish its effect from the natural course by comparison of peritoneal transport before and after infection.

**Participants:** We analysed prospectively collected data from 541 incident peritoneal dialysis (PD) patients, aged > 18 years, between 1990 and 2010. Standard Peritoneal Permeability Analyses (SPA) within the year before and within the year after (but not within 30 days) the first peritonitis were compared. In a control group without peritonitis, SPAs within the first and second year of PD were compared.

**Main outcome measurements:** SPA data included the mass transfer area coefficient of creatinine, glucose absorption and peritoneal clearances of β-2-microglobulin (B2M), albumin, IgG and α-2-macroglobulin (A2M). From these clearances, the restriction coefficient to macromolecules (RC) was calculated. Also, parameters of fluid transport were determined: transcapillary ultrafiltration rate (TCUFR), lymphatic absorption rate (ELAR) and free water transport. Crude and adjusted linear mixed models were used to compare the slopes of peritoneal transport parameters in the peritonitis group to the control group. Adjustments were made for age, sex and diabetes.

**Results:** Of 541 patients, 367 experienced a first peritonitis episode within a median time of 12 months after the start of PD. Of these, 92 peritonitis episodes were preceded and followed by a SPA within one year. Forty-five patients without peritonitis were included in the control group. Logistic reasons (peritonitis group: 48% vs control group: 83%) and switch to hemodialysis (peritonitis group: 22% vs control group: 3%) were the main causes of missing SPA data post-peritonitis and post-control. When comparing the slopes of peritoneal transport parameters in the peritonitis group and the control group, a first peritonitis episode was associated with faster small solute transport (glucose absorption, $p = 0.03$) and a concomitant lower TCUFR ($p = 0.03$). In addition, a discreet decrease in macromolecular transport was seen in the peritonitis group: mean difference in post- and pre-peritonitis values: IgG: $-8 \mu$L/min ($p = 0.01$), A2M: $-4 \mu$L/min ($p = 0.02$), albumin: $-10 \mu$L/min ($p = 0.04$). Accordingly, the RC to macromolecules increased after peritonitis: $0.09, p = 0.04$.

**Conclusions:** The very first peritonitis episode alters the natural course of peritoneal membrane characteristics. The most likely explanation might be that cured peritoneal infection later causes long-lasting alterations in peritoneal transport state.
Introduction

Preservation of peritoneal membrane quality in peritoneal dialysis (PD) patients is required to maintain these patients on PD. Both morphological and functional peritoneal alterations are a consequence of long-term PD treatment. Exposure to glucose and glucose degradation products (GDPs) and the occurrence of peritonitis are proinflammatory stimuli that may cause alterations. Both morphological and functional changes may result in discontinuation of chronic PD treatment. Peritonitis has been hypothesized to be an important cause of peritoneal transport alterations by inflammatory damage. However, only few studies determined the importance of cumulative peritonitis among long-term PD patients by measurements of transport kinetics, and reported inconsistent results. A few studies have shown a temporary effect of peritonitis on small solute transport and net ultrafiltration, which recovered after the acute phase. Others identified a sustained effect of recurrent or severe peritonitis on peritoneal transport characteristics. In contrast, some authors found no association between the occurrence of peritonitis and peritoneal transport status when peritonitis was treated properly or adjustments for time on PD were made. Studies investigating the effects of a single, but not the first, peritonitis episode reported equivocal results. Little or no evidence is available on the impact of the very first peritonitis episode on peritoneal transport characteristics. It is unknown whether the first episode of peritonitis causes permanent peritoneal membrane damage or has only a temporary and reversible effect.

The objective of this study was to investigate the importance of the first peritonitis episode in chronic PD patients by comparison of peritoneal membrane characteristics before and after the infection. To distinguish possible effects from those induced by the duration of PD, a control group without peritonitis was included.

Subjects and methods

We analysed prospectively collected data from 541 incident PD patients, aged > 18 years old, receiving dialysis in a tertiary-care university hospital between January 1990 and July 2010. A peritonitis group and a control group were formed. The peritonitis group included patients experiencing a first peritonitis episode and with a Standard Peritoneal Permeability Analysis (SPA) within the year before (pre-peritonitis SPA) and the next one within the year (but not within 30 days) after their first peritonitis episode (post-peritonitis SPA). The post-peritonitis SPA was performed before the occurrence of a second peritonitis episode. The control group included patients without peritonitis and with a SPA within the first year (pre-
control SPA) and within the second year (post-control SPA) after the start of PD. Pre- and post-peritoneal transport measurements were compared.

**Peritonitis**

All peritonitis episodes during PD treatment were documented. Peritonitis was diagnosed, according to the criteria developed by Vas et al.,\textsuperscript{20} when at least 2 of 3 findings were present: abdominal pain, cloudy effluent with $\geq 100$ white blood cells/µL and 50% polymorphonuclear cells and/or positive microbiological culture of the dialysate. These criteria have been endorsed by the International Society for Peritoneal Dialysis (ISPD) in the current PD-related infection guidelines.\textsuperscript{21} Detailed information including leukocyte counts, microbiology and start and stop dates of peritonitis episodes was collected.

**Standard peritoneal permeability analyses**

Since 1990, a yearly SPA was routinely performed to examine peritoneal transport characteristics.\textsuperscript{22,23} Only SPAs using solutions containing 3.86% glucose were selected for this study. SPA measurements included the mass transfer area coefficient (MTAC) of creatinine, glucose absorption and peritoneal clearances of the following serum proteins: $\beta$-2-microglobulin (B2M), albumin, IgG and $\alpha$-2-macroglobulin (A2M). From these clearances, the restriction coefficient to macromolecules (RC) was calculated.\textsuperscript{24} In addition, parameters of fluid transport were determined in a SPA: transcapillary ultrafiltration, effective lymphatic absorption and free water transport.\textsuperscript{25} The complete SPA procedure and all calculations have thoroughly been described previously by Pannekeet et al.\textsuperscript{22} and Smit and colleagues.\textsuperscript{23,25} From 1997, the measurement and calculation of the biomarker cancer antigen 125 (CA125) and its appearance rates were incorporated in the SPA.

**Statistical analyses**

Differences in baseline characteristics between the peritonitis and control group were tested with an unpaired Student’s t-test, Mann-Whitney (continuous data) or chi-square test (categorical data). An independent sample t-test or Mann-Whitney U test (dependent on the distribution of the data) was used to assess differences between cases and controls on baseline (pre-measurements) and after either the peritonitis or after one year to investigate the natural course (post-measurements). A paired sample t-test or Wilcoxon signed ranks test (dependent on distribution of the data) was performed comparing pre- and post-SPA data. Results are expressed as mean values and standard deviations. Crude and adjusted linear mixed models were performed to distinguish changes within peritoneal transport characteristics, caused by the initial peritonitis episode from those related to the natural course. Adjustments were made for age, sex and diabetes. Results are expressed as crude and adjusted slope differences and 95% confidence intervals (CIs). Data analyses were performed using SPSS 20.0.
First peritonitis alters the natural course of peritoneal transport

Sensitivity analyses

Adjusted linear mixed models were used to investigate whether peritonitis’ characteristics such as timing, causative microorganisms or severity modified the effect of the first peritonitis on peritoneal transport. Early peritonitis was defined as < 1 year after the start of PD and compared with a reference group of late peritonitis, defined as ≥ 1 year after start of PD. Severe peritonitis was defined as a leukocyte count > 1,090 cells/mm³ on day 3 or > 100 cells/mm³ on day 5 of the peritonitis episode and compared with a reference group of less severe peritonitis. Causative microorganisms were dichotomized in Gram-positive microorganisms (not coagulase-negative staphylococci (CNS)) and compared with a reference group that consists of all other causative microorganisms. Results are expressed as adjusted slope differences and 95% CIs.

Results

Population characteristics

Between January 1990 and July 2010, 541 incident PD patients aged 18 and older received dialysis in our department. Of these patients, 367 experienced at least one episode of peritonitis. Of these episodes, 92 were preceded and followed by a SPA within one year and could be selected for inclusion in the peritonitis group. Of the patients without a peritonitis episode, 45 were eligible for inclusion in the control group (Figure 1). Logistic reasons were the main cause for missing SPA data after the first peritonitis episode (48%) and in the controls (83%). In addition, in the peritonitis group, switch to hemodialysis (22%), death (22%) and receiving a transplant (8%) within one year after the first peritonitis episode accounted for the rest of the missing SPA data. In the control group, only a minority of missing post-SPA data could be explained by patients who changed modality (3%), died (7%) or received a transplant (7%) within the second year of PD treatment. The baseline characteristics of the study population are summarized in Table 1. The peritonitis and control group were similar at baseline with respect to age, percentage of males and diabetics and the distribution of causes of end-stage renal disease (ESRD). No differences in baseline characteristics were observed when patients included in the present study were compared with all patients eligible for the study.
Figure 1. Flow chart of patient selection in peritonitis and control group.

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients included in the present study</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peritonitis group</td>
<td>Control group</td>
<td></td>
</tr>
<tr>
<td>Patients (n)</td>
<td>92</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Age start dialysis (median; range)</td>
<td>51 (21-78)</td>
<td>55 (25-78)</td>
<td>0.30</td>
</tr>
<tr>
<td>Male (%)</td>
<td>49</td>
<td>60</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>24</td>
<td>22</td>
<td>0.77</td>
</tr>
<tr>
<td>Cause of ESRD (%)</td>
<td></td>
<td></td>
<td>0.85</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>16</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>16</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>44</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ESRD, end-stage renal disease. No significant differences between the included and excluded peritonitis group; no significant differences between the included and excluded controls.

**Pre-and post-SPA measurements**

Pre- and post-SPA measurements were compared in the peritonitis and in the control group. Results are shown in Table 2. Median time on PD to pre-measurements was 5.1 months in the peritonitis group and 4.1 months in the control group (p = 0.10). The median time to post-measurements was 17.8 months in the peritonitis group and 16.6 months in the control group (p = 0.38). The mean time between a pre-SPA and a post-SPA was 11.9 months in the peritonitis group and 12.6 months in the control group, which was not different (p = 0.19). No differences were found between pre-peritonitis and pre-control group SPAs. In the peritonitis group, no significant decrease of low molecular weight solute transport was found, whereas in the control group a decrease was present (p < 0.001). A concomitant
increase in transcapillary ultrafiltration \( (p = 0.04) \), lymphatic absorption \( (p = 0.01) \) and decrease in the percentage of free water transport \( (p = 0.01) \) was seen in the control group, whereas this was absent in the peritonitis group. A discreet, but significant, decrease in the transport of macromolecules was found after the first peritonitis episode. The mean differences between post- and pre-peritonitis values were IgG: \(-8 \text{ μL/min} \quad (p = 0.01)\), A2M: \(-4 \text{ μL/min} \quad (p = 0.02)\), albumin: \(-10 \text{ μL/min} \quad (p = 0.04)\). Also, the restriction coefficient to macromolecules increased after peritonitis: \(0.09, \quad p = 0.04\). These significant differences in macromolecular transport and the RC were not observed in the control group. Finally, the CA125 appearance rates after the first peritonitis episode were significantly lower compared with the control group \( (p < 0.001)\).

### Table 2. Comparison of pre- and post-peritoneal transport status in the peritonitis and control group

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>n=92 Pre-peritonitis SPA</th>
<th>Mean±SD</th>
<th>n=92 Post-peritonitis SPA</th>
<th>Mean±SD</th>
<th>n=45 Pre-Control SPA</th>
<th>Mean±SD</th>
<th>n=45 Post-Control SPA</th>
<th>Mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTAC creatinine (mL/min)(^a)</td>
<td>10.7±3.6</td>
<td>10.2±3.0</td>
<td>0.27</td>
<td>11.8±4.3</td>
<td>10.1±3.3</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose absorption (%)(^a)</td>
<td>64±11</td>
<td>61±10</td>
<td>0.11</td>
<td>65±11</td>
<td>58±10</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2M clearance (mL/min)(^b)</td>
<td>1.2±0.5</td>
<td>1.1±0.4</td>
<td>0.09</td>
<td>1.3±0.5</td>
<td>1.1±0.4(^d)</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin clearance (mL/min)(^b)</td>
<td>0.10±0.05</td>
<td>0.09±0.04</td>
<td>0.04</td>
<td>0.10±0.04</td>
<td>0.09±0.04</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgG clearance (μL/min)(^b)</td>
<td>57±34</td>
<td>51±28</td>
<td>0.01</td>
<td>62±32</td>
<td>51±24</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A2M clearance (μL/min)(^b)</td>
<td>21±16</td>
<td>20±33</td>
<td>0.02</td>
<td>24±19</td>
<td>21±12</td>
<td>0.44</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restriction coefficient(^a)</td>
<td>2.41±0.38</td>
<td>2.50±0.34</td>
<td>0.04</td>
<td>2.41±0.34</td>
<td>2.38±0.30</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELAR (mL/min)(^b)</td>
<td>1.57±1.03</td>
<td>1.55±0.96</td>
<td>0.67</td>
<td>1.79±0.93</td>
<td>1.42±0.77</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCUFR (mL/min)(^b)</td>
<td>3.51±1.57</td>
<td>3.32±1.37</td>
<td>0.35</td>
<td>3.36±1.41</td>
<td>3.79±1.31</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free water transport (%)(^a)</td>
<td>31.6±12.1</td>
<td>28.8±19.8</td>
<td>0.82</td>
<td>29.1±12.6</td>
<td>28.9±17.7</td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AR-CA125 (U/min)(^c)</td>
<td>129.4±85.3</td>
<td>105.9±70.1(^d)</td>
<td>0.07</td>
<td>153.7±105.0</td>
<td>172.3±119.4</td>
<td>0.83</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SPA, standard peritoneal permeability analysis; MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate. AR-CA125, appearance rate CA125. \(^a\)Paired sample \( t \)-test; \(^b\)Paired Wilcoxon signed ranks test. \(^c\)Ca125 measurements from 1997. \(^d\)Significantly lower than the post-control SPA. Mean and standard deviations are given.

### The effect of the first peritonitis episode compared with the natural course

A comparison between the slope of peritoneal transport parameters in the peritonitis group and the control group was made. Crude and adjusted slope differences are shown in Table 3. After a first peritonitis episode, patients had a positive time course of glucose absorption, leading to an increase (adjusted slope difference: \(5, 95\% \text{ CI}: 1 – 9; \quad p = 0.03\)) and a negative time course of transcapillary ultrafiltration, leading to a decrease (adjusted slope difference: \(-0.58, 95\% \text{ CI}: -1.09 \text{ to } -0.07; \quad p = 0.03\)) when compared with the controls. The very first peritonitis episode did not significantly affect protein clearances and its restriction coefficient, lymphatic absorption, free water transport and the CA125 appearance rate.
However, all parameters followed the direction of an enhanced transport state after the first peritonitis episode compared with the natural course.

### Table 3. Comparison of the rate of change in the transport parameter in the peritonitis group \((n=92)\) compared with the control group \((n=45)\)

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Crude slope difference</th>
<th>p-value</th>
<th>Adjusted(^a) slope difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(95% Confidence interval)</td>
<td></td>
<td>(95% Confidence interval)</td>
<td></td>
</tr>
<tr>
<td>MTAC creatinine ((\text{mL/min}))</td>
<td>1.27 (-0.16–2.71)</td>
<td>0.08</td>
<td>1.10 (-0.34–2.53)</td>
<td>0.13</td>
</tr>
<tr>
<td>Glucose absorption ((%))</td>
<td>5 (1–9)</td>
<td>0.02</td>
<td>5 (1–9)</td>
<td>0.03</td>
</tr>
<tr>
<td>B2M clearance ((\text{mL/min}))</td>
<td>0.06 (-0.13–0.25)</td>
<td>0.52</td>
<td>0.06 (14–0.25)</td>
<td>0.57</td>
</tr>
<tr>
<td>Albumine clearance ((\text{mL/min}))</td>
<td>-0.01 (-0.02–0.02)</td>
<td>0.76</td>
<td>-0.01 (-0.02–0.01)</td>
<td>0.70</td>
</tr>
<tr>
<td>IgG clearance ((\mu\text{L/min}))</td>
<td>3 (-10–16)</td>
<td>0.65</td>
<td>3 (-11–17)</td>
<td>0.69</td>
</tr>
<tr>
<td>A2M clearance ((\mu\text{L/min}))</td>
<td>-1 (-7–5)</td>
<td>0.70</td>
<td>2 (-9–4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>0.10 (-0.04–0.24)</td>
<td>0.16</td>
<td>0.14 (-0.01–0.27)</td>
<td>0.06</td>
</tr>
<tr>
<td>ELAR ((\text{mL/min}))</td>
<td>0.36 (-0.05–0.77)</td>
<td>0.08</td>
<td>0.30 (-0.11–0.72)</td>
<td>0.15</td>
</tr>
<tr>
<td>TCUFR ((\text{mL/min}))</td>
<td>-0.59 (-1.09–0.09)</td>
<td>0.02</td>
<td>-0.58 (-1.09–0.07)</td>
<td>0.03</td>
</tr>
<tr>
<td>Free water transport ((%))</td>
<td>-5.9 (-12.7–0.9)</td>
<td>0.09</td>
<td>-5.2 (-12.1–1.7)</td>
<td>0.14</td>
</tr>
<tr>
<td>AR-CA125 ((\text{U/min}))(^b)</td>
<td>-2.53 (-7.39–2.33)</td>
<td>0.30</td>
<td>-2.81 (-7.71–2.09)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Abbreviations: SPA, standard peritoneal permeability analysis; MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate. AR-CA125, appearance rate CA125. Linear mixed models were performed with the control group as the reference group. \(^a\)Adjusted for age, sex and diabetes. \(^b\)CA125 measurements from 1997.

### Timing, severity and causative microorganism

Several characteristics of a peritonitis episode theoretically can modify the effect on peritoneal transport (Table 4). Sensitivity analyses were performed to investigate whether the time of occurrence after the start of PD, its causative microorganisms and the severity of the episodes were potential modifiers (Table 5). The timing of the first peritonitis episode did not alter the association with peritoneal transport. A severe first peritonitis was associated with decreased lymphatic absorption (adjusted slope difference: -0.76, 95% CI: -1.40 to -0.11; \(p = 0.02\)) when compared with less severe peritonitis, but not with other parameters of fluid transport. A first peritonitis episode caused by gram-positive microorganisms (not CNS) was associated with enhanced transport of low molecular weight solutes and an increased lymphatic absorption (adjusted slope difference: 0.59, 95% CI: 0.06 – 1.12; \(p = 0.03\)) compared with peritonitis episodes caused by other microorganisms.
First peritonitis alters the natural course of peritoneal transport

Table 4. Characteristics of the peritonitis episodes (n=92)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months after the start of PD (median; IQR)</td>
<td>12 (7–24)</td>
</tr>
<tr>
<td>Peritonitis in the first year (%)</td>
<td>53</td>
</tr>
<tr>
<td>Peritonitis in the second year (%)</td>
<td>24</td>
</tr>
<tr>
<td>Peritonitis in the third year or later (%)</td>
<td>22</td>
</tr>
<tr>
<td>Severity (n (%))</td>
<td></td>
</tr>
<tr>
<td>Leukocyte count &gt;1,090 cells/mm³ day 3</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Leukocyte count &gt;100 cells/mm³ day 5</td>
<td>13 (14)</td>
</tr>
<tr>
<td>&gt; 1,090 cells/mm³ day 3 or &gt;100 cells/mm³ day 5</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Causative microorganism (n (%))</td>
<td></td>
</tr>
<tr>
<td>Gram-positive</td>
<td>53 (58)</td>
</tr>
<tr>
<td>Gram-negative</td>
<td>14 (15)</td>
</tr>
<tr>
<td>Culture-negative</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Other</td>
<td>17 (18)</td>
</tr>
</tbody>
</table>

Abbreviations: PD, peritoneal dialysis; IQR, interquartile range.

Discussion

The results of the present study show that after the recovery from the very first peritonitis episode, patients remain at a relatively faster peritoneal transport state compared with patients who were peritonitis-free. This was represented by faster transport rates of low molecular weight solutes and less efficient fluid transport in the peritonitis group compared with the natural course.

Previously, Del Peso et al.26 have shown a decreasing MTAC creatinine and increasing ultrafiltration within the first year after the start of dialysis. Similar to our findings, this was not present in patients suffering from peritonitis. Furthermore, Struijk et al.27 have found that after the start of PD, patients present with fast transport of low molecular weight solutes and inefficient ultrafiltration. This indicates an initial effect of the start of PD itself on peritoneal transport. However, after a period of 5 months, stabilization of peritoneal function towards a slower peritoneal transport state was observed. In our study, patients who experienced a first peritonitis episode remained “so-called” faster transporters of small solutes and fluids compared with patients without peritonitis. The latter showed a significant decline in small solute transport and an increase in the efficiency of fluid transport. The relatively faster transport state after the first peritonitis episode might be explained by low-grade inflammatory damage to the peritoneum. Peritoneal inflammation induces neovascularization, which increases the effective peritoneal surface area and reduces the osmotic conductance to glucose. An alternative explanation might be the slight, but not significant, difference between the time from the start of dialysis to the pre- and post-measurements that were compared. Although unlikely, an influence on the difference in the observed transport state cannot be excluded with certainty.
Table 5. The adjusted slope differences per peritonitis group stratified by characteristics of the peritonitis episode

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Peritonitis group stratified by timing of peritonitis</th>
<th>Peritonitis group stratified by severity of peritonitis</th>
<th>Peritonitis group stratified by microorganism of peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted slope difference (95% CI)</td>
<td>Adjusted slope difference (95% CI)</td>
<td>Adjusted slope difference (95% CI)</td>
</tr>
<tr>
<td>MTAC creatinine (mL/min)</td>
<td>-1.11 (-2.94–0.72)</td>
<td>1.14 (-1.19–3.46)</td>
<td>2.24 (0.29–4.19)</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>-4 (-9–1)</td>
<td>-4 (-11–2)</td>
<td>6 (1–12)</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>-0.06 (-0.22–0.11)</td>
<td>-0.29 (-0.50–0.09)</td>
<td>0.01 (-0.17–0.18)</td>
</tr>
<tr>
<td>ELAR (mL/min)</td>
<td>0.17 (-0.34–0.68)</td>
<td>-0.76 (-1.40– -0.11)</td>
<td>0.59 (0.06–1.12)</td>
</tr>
<tr>
<td>TCUFR (mL/min)</td>
<td>-0.09 (-0.70–0.51)</td>
<td>-0.65 (-1.43–0.13)</td>
<td>-0.08 (-0.73–0.57)</td>
</tr>
<tr>
<td>Free water transport (%)</td>
<td>5.4 (-3.2–14.0)</td>
<td>-6.2 (-16.8–4.4)</td>
<td>-6.0 (-15.1–3.1)</td>
</tr>
</tbody>
</table>

Abbreviations: SPA, standard peritoneal permeability analysis; CI, confidence interval; MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate; CNS, coagulase-negative staphylococci. *Adjusted linear mixed models were performed. Early peritonitis (n=48) was defined as <1 year after the start of PD and compared with a reference group of late peritonitis defined as ≥1 year after start of PD. Severe peritonitis (n=16) was defined as a leukocyte count >1,090 cells/mm³ on day 3 or >100 cells/mm³ on day 5 of the peritonitis episode compared with a reference group of less severe peritonitis. *Gram-positive microorganisms (not CNS) compared with a reference group of all other causative microorganisms. *Adjusted for age, sex and diabetes.
We hypothesized that the timing of peritonitis after the start of PD, the severity of the peritonitis episode and the microorganism causing the peritonitis might be potential modifiers of the effect of the first peritonitis on peritoneal transport characteristics. Previously, a study in 16 patients by Selgas et al. showed that peritoneal transport characteristics were influenced by peritonitis only after more than 3 years on PD. In addition, Fusshöller et al. found that peritoneal transport characteristics are correlated with the time on PD. However, in the present study, time on PD did not alter the effect of the first peritonitis. An explanation might be that the majority of the peritonitis episodes occurred in the first year after the start of PD. Previously, Davies et al. showed that the severity of recurrent peritonitis, in terms of leukocyte count, and the identification of their causative microorganisms was associated with a larger change in small solute transport and ultrafiltration. However, this was not found in single, but not the first, isolated episodes of peritonitis. In contrast, Hung et al. studied the first peritonitis episode and found an association between the identification of the causative microorganism and an increase in small solute transport. In addition, culture-negative peritonitis showed less impact on peritoneal transport compared with culture-positive peritonitis. In the present study, the severity of the peritonitis episode altered the association with lymphatic absorption, but not with other parameters of fluid transport. Furthermore, gram-positive microorganisms, when compared with all other microorganisms, enhanced the association with increased low molecular weight solute transport and increased lymphatic absorption, but not with other parameters of fluid transport.

Although the increasing time course of the restriction coefficient could not be distinguished from the natural course, to the best of our knowledge, the present study is the first to identify an increase in peritoneal size-selectivity to macromolecules after a first peritonitis episode. An earlier study among prevalent PD patients, by Zemel et al. showed no difference in the restriction coefficient directly prior to the development of peritonitis compared with the value after recovery. A decreased value was only present during the first two days of acute peritonitis. These findings suggest that an increase of the restriction coefficient after the first peritonitis episode takes some time to develop.

Several reasons may explain why previous studies were unable to identify changes in macromolecular transport after a single peritonitis episode. First of all, individual proteins were not determined and the concomitant restriction coefficient was not calculated. Furthermore, studies were mainly carried out in prevalent dialysis patients in which time on PD might have a major influence on peritoneal transport characteristics before and after peritonitis. In addition, studies compared peritoneal transport characteristics after peritonitis with unstable transport characteristics during peritonitis or did not exclude transport measurements during the inflammatory phase after peritonitis. Moreover, some studies did not compare two transport measurements conducted from the same
patient at all. Lastly, the earliest studies have been performed during a period with higher incidences of peritonitis. We hypothesize that the large number of peritonitis episodes during the earlier days of PD may have masked local changes due to a single peritonitis. A possible biological explanation for the discreet difference in peritoneal size-selectivity to macromolecules might be that changes are caused in the radius of the large pores as described in the “three-pore model” by Rippe and Stelin. Lai et al. showed that the number of macrophages, released cytokines and attracted leukocytes are elevated in the peritoneal cavity at least six weeks regardless of clinical remission of peritonitis. However, in general, studies found that these numbers return to baseline shortly after the recovery from peritonitis. Also in the present study, when the peritonitis group was compared with the control group, the changes in macromolecular transport and the restriction coefficient could not be distinguished from the natural course. Therefore, increased peritoneal vascular surface area (defined as the MTAC creatinine) rather than the intrinsic permeability of the membrane (restriction coefficient) may cause changes in macromolecular transport. Interestingly, after the very first peritonitis episode, we identified a significantly lower appearance rate of CA125 compared with the control group. A previous in-vitro study by Breborowicz et al., emphasized that the amount of CA125 released from mesothelial cells is not a good index of the number or properties of mesothelial cells. However, other patient based studies, have shown that levels of CA125 in peritoneal effluent are highly elevated during peritonitis. This can be explained by the induction of necrosis of mesothelial cells during peritonitis, which enhances CA125 appearance rate. Moreover, it has been suggested both in-vitro and in-vivo, that peritonitis might induce irreversible loss of mesothelial cells and therefore CA125 levels might be permanently lower after recovery from peritonitis. None of the above-cited studies was able to confirm this hypothesis. In addition, time on PD was found to be an important determinant of CA125 effluent levels. When compared with the natural course, the enhanced loss of mesothelial cell mass could not be attributed to the first peritonitis episode with certainty.

There are some limitations of the present study that need to be addressed. First, the inclusion of the patients in the peritonitis group was highly dependent on whether SPA measurements were performed before and after the peritonitis episode. When a patient suffered from a severe peritonitis episode causing termination of PD treatment or death, no SPA measurement after the infection was available and the patient was not included in the analysis. The percentage of patients missing SPA data due to switch to hemodialysis or death was consistent with previous literature. The majority of the missing SPA data could be attributed to logistic reasons, which may result from unmeasured patient-related or facility-related factors where no SPA was planned or the SPA was cancelled for unknown reasons. Therefore, although the majority of the missing SPA data could be contributed to logistic reasons, there may have been selection bias towards the inclusion of probably
First peritonitis alters the natural course of peritoneal transport

healthier patients surviving a potentially less severe peritonitis episode. Patients in the control group needed to survive the first two years of PD as well, including their first two SPA measurements, to be eligible for inclusion. This resulted in a relatively healthy control group representing the stable long-term PD patient as well. Therefore, we underline that the same selection process was used in the peritonitis group and in the control group and no differences between both groups were found at baseline in terms of peritoneal transport characteristics or baseline demographics. In addition, the percentage of patients excluded from the study because of insufficient SPA data was similar in both groups. Therefore, we emphasize that, if of any importance, this selection is more likely to have led to an underestimation of the effect of peritonitis on peritoneal transport characteristics and that the influence of a severe first peritonitis episode might be even larger.

Great improvements in PD solutions have been made over the last decades. In our dialysis unit, patients were treated with Dianeal between 1990 and 1997, with Dianeal or Physioneal between 1998 and 2004, and with Physioneal between 2005 and 2010. The use of icodextrin started in 1997. Exposure to glucose and glucose degradation products may have influenced peritoneal host defense or the effect of the peritonitis episode on the peritoneal membrane. Unfortunately, our study is underpowered to perform a stratified analysis and data for exact calculations of exposure to glucose and glucose degradation products during dialysis treatment are unavailable.

One of the strengths of this study is the large number of patients with repeated SPAs that have been prospectively collected as a part of routine clinical care. The large amount of data collected enabled us to form a peritonitis and control group. Moreover, we could analyse peritoneal transport characteristics before and after the acute proinflammatory phase of peritonitis and observe long-lasting effects. Furthermore, all patients in the study were incident to dialysis. Peritonitis episodes were thoroughly documented in an extensive peritonitis database. Lastly, SPAs were used to determine peritoneal transport characteristics, which is advantageous to the Peritoneal Equilibration Test (PET). A SPA provides additional information on pathways of fluid transport and includes the peritoneal clearances of several serum proteins from which the RC can be calculated.24

In conclusion, the present study has confirmed that the very first peritonitis episode influences the natural course of peritoneal transport characteristics. We have shown that patients who experienced a cured first peritonitis episode later remain at a faster transport state compared with patients without peritonitis. The most likely explanation for these findings might be that cured peritoneal infection may lead to a latent state that later causes long-lasting alterations. These results do not have direct implications for clinical practice. However, the present study provides new insights into the effect of peritonitis on peritoneal transport characteristics. In addition, this study helps to gain better understanding of the peritoneal membrane and peritoneal transport in general, which may contribute to future improvements of PD therapy.
References

First peritonitis alters the natural course of peritoneal transport


Chapter 8

The mutual relationship between peritonitis and peritoneal transport

Sadie van Esch*, Anouk T.N. van Diepen*, Dirk G. Struijk, Raymond T. Krediet
*These authors contributed equally to the manuscript

Peritoneal Dialysis International 2014, in press
Abstract

Background: Preservation of the peritoneum is required for long-term peritoneal dialysis (PD). We investigated the effect of multiple peritonitis episodes on peritoneal transport.

Methods: Prospectively collected data from 479 incident PD patients treated between 1990 and 2010 were analysed, using strict inclusion criteria: follow-up of at least 3 years with the availability of a Standard Peritoneal permeability Analysis (SPA) in the first year after start of PD and within the third year of PD, without peritonitis preceding the first SPA. For the purpose of the study, we only included patients who remained peritonitis free \( n=28 \) or who had 3 or more peritonitis episodes \( n=16 \).

Results: At baseline the groups were similar with regard to small solute and fluid transport. However, the frequent peritonitis group had lower peritoneal protein clearances compared with the no peritonitis group, resulting in lower dialysate concentrations of proteins: albumin 196.5 mg/L versus 372.5 mg/L, IgG 36.4 mg/L versus 65.0 mg/L, and α-2-macroglobulin 1.9 mg/L versus 3.6 mg/L, \( p<0.01 \). No differences in serum concentrations were present. A comparison between the transport slopes over time in both groups showed a positive time trend of mass transfer area coefficient (MTAC) creatinine \( p=0.03 \) and glucose absorption \( p=0.09 \) and a negative trend of transcapillary ultrafiltration \( p=0.06 \), when compared with the no peritonitis group. Frequent peritonitis did not affect free water transport.

Conclusions: Slow initial peritoneal transport rates of serum proteins result in lower dialysate concentrations, and likely a lower opsonic activity, which is a risk factor for peritonitis. Patients with frequent peritonitis show an increase in small solute transport and a concomitant decrease of ultrafiltration. In long-term peritonitis-free PD patients small solute transport decreased, whereas ultrafiltration increased. This suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area without all the structural membrane alterations that may develop after long-term PD.
Introduction

Structural and functional integrity of the peritoneum is of crucial importance for successful peritoneal dialysis (PD). However, in some long-term PD patients, treatment is associated with morphologic and functional peritoneal alterations. It is well-known that acute peritonitis causes temporary changes in peritoneal transport parameters, like increased solute transport and protein loss, leading to ultrafiltration failure. This is observed both during intermittent PD and continuous ambulatory PD (CAPD). In CAPD these phenomena return to normal values within two weeks after cure of the infection, parallel to the locally produced vasoactive substances, causing them.

Studies on permanent effects of peritonitis on peritoneal transport have shown inconsistent results. Some studies showed no effect, whereas others demonstrated a clear consequence of peritonitis on peritoneal membrane function. Some researchers only found a change in peritoneal transport after a severe peritonitis or after frequent peritonitis episodes. However, all these studies suffered the lack of a control group representing the natural course.

In a recent study, we investigated the possible effect of the very first peritonitis episode on peritoneal transport characteristics in new PD patients and distinguished its effect from the natural course. Patients who experienced a first peritonitis episode, later remained at a faster transport state compared with patients without peritonitis. In addition, a decrease in macromolecular transport and an increase in its size-selectivity was found. Previously, Del Peso et al. have shown a decreasing MTAC creatinine and increasing ultrafiltration within the first year after the start of dialysis. Similar to our findings, this was not present in patients who suffered peritonitis.

Controversy exists about the impact of frequent peritonitis on peritoneal transport characteristics. Therefore, the aim of the present study was to make a comparison of peritoneal transport characteristics between incident PD patients with more than three peritonitis episodes during a follow-up of three years, and a control group of similar patients who did not experience any peritonitis episode before and during the same follow-up time.

Patients and methods

Patients

Between 1990 and 2010, all adult patients starting PD in a tertiary-care university hospital were included in the study. Data about peritonitis episodes and peritoneal transport characteristics were collected prospectively in a large database. We compared a Standard Peritoneal permeability Analysis (SPA) in the first year after start of PD (‘baseline’) and a
SPA within the third year of PD (‘late’). Patients either had to remain peritonitis-free or experienced three or more peritonitis episodes during the three year follow-up period. Data were excluded from the analyses, when peritonitis preceded the baseline SPA or when a SPA was performed within the acute phase of 30 days after peritonitis (Figure 1). Patients were treated with Dianeal (Baxter Healthcare S.A., Castlebar, Ireland) between 1990 and 1997, with Dianeal or Physioneal (Baxter Healthcare S.A., Castlebar, Ireland) between 1998 and 2004, and with Physioneal between 2005 and 2010. The use of icodextrin started in 1997.

**Figure 1. Study design.** *The “late” SPA was never done within 30 days after an episode of acute peritonitis.*

**Peritonitis**

Peritonitis was diagnosed when at least two of three findings were present: clinical symptoms, effluent cell count > 100 cells/μL and a positive culture of the dialysate. These criteria have been developed by Vas and adopted by the current guidelines of the International Society of Peritoneal Dialysis (ISPD). All episodes were treated empirically with a first-generation cephalosporin, which was combined with gentamicin when the patient was clinically ill and needed hospitalization. Antibiotic treatment thereafter could be adjusted according to the resistance of the causative organism. Treatment duration was 1 week after cultures had become negative and cell counts reached less than 100 cells/μL. The previously described protocol was published in 1985 and has not been changed since.

**Standard peritoneal permeability analyses (SPA)**

Since 1990 a SPA was performed yearly to assess peritoneal transport characteristics. Only SPA’s using solutions containing 3.86% glucose were selected for this study. SPA measurements included the mass transfer area coefficient (MTAC) of creatinine, the percentage glucose absorption and peritoneal clearances of serum proteins β-2-microglobulin (B2M), albumin, IgG and α-2-macroglobulin (A2M). The restriction coefficient to macromolecules (RC) was calculated from these clearances. It represents the size-selectivity of the peritoneal membrane.
membrane, i.e. the average large pore radius. In addition, parameters of fluid transport were determined: transcapillary ultrafiltration, effective lymphatic absorption, and free water transport. All calculations were performed as previously described by Pannekeet et al. and Smit and collegues.17,19

Statistical analyses
An independent Student’s t-test, Mann-Whitney (continuous data) or chi-square test (categorical data) was used to assess differences in baseline clinical characteristics and baseline SPA measurements between the group without peritonitis and the frequent peritonitis group. To compare baseline and late measurements in individual patients, a paired sample T-test or Wilcoxon signed ranks test (dependent on the distribution of the data) was used. Results are expressed as mean values and standard deviations, or as median values with interquartile range. Crude and adjusted linear mixed models were performed to differentiate between changes in peritoneal transport characteristics caused by frequent peritonitis episodes, from the possible effects caused by PD duration itself. Adjustments were made for age and diabetes. Results are expressed as crude and adjusted slope differences and 95% confidence intervals. Data analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).

Sensitivity analyses
Adjusted linear mixed models were used to investigate whether the time period of start of PD, the number of peritonitis episodes, or the severity of peritonitis modified the effect of peritonitis on peritoneal transport. For this purpose only, a group with 1 or 2 peritonitis episodes (intermediate) was added. The patient cohort was stratified by the time period PD was started: time period 1990-2000 or 2000-2010. Severe peritonitis was specified as one or more peritonitis episodes with a leukocyte count >1,090 cells/mm³ on day 3 or >100 cells/mm³ on day 5 of the peritonitis episode and compared with a reference group of less severe peritonitis. Results are expressed as adjusted slope differences and 95% CIs. A separate analysis could not be done for the kind of dialysis solution used, because of the small number of patients in the various subgroups.

Results
Population characteristics
Between 1990 and 2010, 479 adult patients started PD in our center. Of these patients, 435 patients were excluded. More than half of the patients had an insufficient time of follow-up on PD, 31% had missing SPA data, 3% had an episode of peritonitis before the first SPA
and 5% had only one or two episodes of peritonitis. Eventually, 44 patients were included in the analysis, 28 patients who remained peritonitis-free and 16 patients who experienced three or more episodes of peritonitis (Figure 2). The baseline characteristics are summarized in Table 1. Both groups were similar at baseline with respect to age, percentage of males, distribution of causes of end-stage renal disease (ESRD), the Davies comorbidity score, treatment modality and time period of start of PD. No differences in baseline characteristics (age, sex, and cause of ESRD) were found between the excluded and included patients in this study.

Change in peritoneal transport status from baseline to late per group

Table 2 shows a comparison of baseline and late peritoneal transport parameters per group. The no peritonitis group, in which the natural time-course is reflected, showed a significant decrease from baseline to late in PD treatment for MTAC creatinine ($p=0.01$) and glucose absorption ($p=0.03$), accompanied by an increasing trend for transcapillary ultrafiltration ($p=0.09$). No differences were observed for the protein clearances, effective lymphatic absorption, or free water transport. In contrast, only a significant increase was found for the clearance of albumin in the frequent peritonitis group.

![Flow chart patient selection](image)

**Figure 2. Flow chart patient selection.** The reasons for insufficient follow-up include death, transplantation or transfer to hemodialysis.
Comparison of baseline and late peritoneal transport status between the groups
A comparison between the no peritonitis group and the frequent peritonitis group at the baseline SPA and at the late SPA is shown in Table 2. Median time on PD to the baseline SPA was 5 months in the no peritonitis group and 4 months in the frequent peritonitis group, $p=0.11$. Median time to a late SPA was 39 months in both groups, $p=0.72$. The median time between a baseline SPA and a late SPA was 35 months in the group without peritonitis and 36 months in the frequent peritonitis group, $p=0.28$.

No differences between the no peritonitis group and the frequent peritonitis group were observed at baseline for small solute transport, transcapillary ultrafiltration, lymphatic absorption, and free water transport. However, at baseline, peritoneal clearances of the serum proteins albumin ($p=0.02$), IgG ($p=0.01$), and A2M ($p=0.02$) were significantly lower in the frequent peritonitis group compared with the no peritonitis group, with a concomitant higher restriction coefficient to macromolecules.

Table 1. Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No peritonitis</th>
<th>Frequent peritonitis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14 : 14</td>
<td>10 : 6</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean age (yrs) at start PD</td>
<td>55 ± 14</td>
<td>50 ± 14</td>
<td>0.34</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>4</td>
<td>0.34</td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>9</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Davies comorbidity score (%)</td>
<td></td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>0 comorbidities</td>
<td>29</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>1-2 comorbidities</td>
<td>54</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>≥ 3 comorbidities</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Treatment modality (APD:CAPD)</td>
<td>6 : 22</td>
<td>5 : 11</td>
<td>0.47</td>
</tr>
<tr>
<td>Residual GFR at baseline, estimated by serum β-2-microglobulin (mg/L)</td>
<td>19.4 ± 8.2</td>
<td>23.8 ± 7.9</td>
<td>0.11</td>
</tr>
<tr>
<td>Time from start PD to baseline SPA in months (median (IQR))</td>
<td>5 (4-6)</td>
<td>4 (3-6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Time from start PD to late SPA in months (median (IQR))</td>
<td>39 (32-41)</td>
<td>39 (33-41)</td>
<td>0.72</td>
</tr>
<tr>
<td>Time between baseline and late SPA (median (IQR))</td>
<td>35 (26-36)</td>
<td>36 (27-37)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; IQR, interquartile range.
No differences were present in the plasma concentrations of these proteins to explain the difference in clearances between the groups at baseline. However, the dialysate concentrations of the macromolecules at baseline were significantly ($p<0.01$) lower in the frequent peritonitis group compared with the no peritonitis group, median: albumin 196.5 mg/L versus 372.5 mg/L, IgG 36.4 mg/L versus 65.0 mg/L, and A2M 1.9 mg/L versus 3.6 mg/L. No significant increase of dialysate IgG was found in the group without peritonitis (Figure 3, panel A), whereas in the frequent peritonitis group an increase was present from baseline to late in PD treatment (Figure 3, panel B, $p=0.04$).

Table 2. Comparison of baseline and late peritoneal transport parameters between the group without peritonitis and the group with frequent peritonitis episodes

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Baseline SPA</th>
<th>Late SPA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No peritonitis</td>
<td>Frequent peritonitis</td>
</tr>
<tr>
<td>MTAC creatinine (ml/min)</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td></td>
<td>11.8 ± 4.1</td>
<td>10.0 ± 3.2</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>64 ± 10</td>
<td>61 ± 10</td>
</tr>
<tr>
<td>Clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2M (ml/min)</td>
<td>1.2 ± 0.5</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Albumin (ml/min)</td>
<td>0.11 ± 0.05</td>
<td>0.07 ± 0.03a</td>
</tr>
<tr>
<td>IgG (µl/min)</td>
<td>59 ± 30</td>
<td>36 ± 16a</td>
</tr>
<tr>
<td>A2M (µl/min)</td>
<td>23 ± 20</td>
<td>11 ± 7a</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>2.39 ± 0.32</td>
<td>2.64 ± 0.34c</td>
</tr>
<tr>
<td>ELAR (ml/min)</td>
<td>1.53 ± 0.75</td>
<td>1.48 ± 0.55</td>
</tr>
<tr>
<td>TCUFR (ml/min)</td>
<td>3.0 ± 1.56</td>
<td>3.91 ± 1.50</td>
</tr>
<tr>
<td>Free water transport 0-60min (ml)</td>
<td>123.3 ± 65.0</td>
<td>141.5 ± 62.4</td>
</tr>
</tbody>
</table>

Abbreviations: MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate. $^a$Significantly different ($p<0.05$) between no peritonitis and frequent peritonitis group, either at baseline or after 3 years. $^b$Significantly lower than the baseline SPA of the no peritonitis group. $^c$Significantly higher than the baseline SPA of the frequent peritonitis group.

Late in PD treatment, the differences in dialysate concentrations of serum proteins between the groups were not present anymore. Comparison of late SPA measurements between the groups showed only a significantly lower effective lymphatic absorption ($p=0.04$) in the frequent peritonitis group.

The effect of frequent peritonitis episodes compared with the natural course

A comparison between the slope of peritoneal transport characteristics in the frequent peritonitis group and the group without peritonitis was made. Table 3 shows crude and adjusted slope differences. This is further illustrated in Figure 4. After frequent peritonitis episodes, patients had a positive time course of MTAC creatinine and glucose absorption,
leading to an increase, when compared with patients without peritonitis (MTAC creatinine: adjusted slope difference: 3.04, 95%CI: 0.40 – 5.67, p=0.03; glucose absorption: adjusted slope difference: 6, 95%CI: -1 – 14, p=0.09). This was accompanied by a negative time course of transcapillary ultrafiltration, leading to a decrease (adjusted slope difference: -0.81, 95%CI: -1.63 – 0.02, p=0.06), when compared with the group without peritonitis. Also, patients in the frequent peritonitis group had a positive time course of the protein clearances B2M and albumin, leading to an increase in comparison with the patients without peritonitis (B2M: adjusted slope difference: 0.30, 95%CI: -0.003 – 0.60; p=0.05, albumin: adjusted slope difference: 0.04, 95%CI: 0.005 – 0.07; p=0.02). Frequent peritonitis episodes did not significantly affect the time course of IgG and A2M clearances, lymphatic absorption and free water transport.

Table 3. Comparison of the rate of change in transport parameters in the frequent peritonitis group (n=16) compared with the no peritonitis group (n=28)

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Crude slope difference (95% CI)</th>
<th>p-value</th>
<th>Adjusted* slope difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTAC creatinine (ml/min)</td>
<td>3.47 (1.01 – 5.93)</td>
<td>0.01</td>
<td>3.04 (0.40 – 5.67)</td>
<td>0.03</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>8 (0.2 – 15)</td>
<td>0.04</td>
<td>6 (-1 – 14)</td>
<td>0.09</td>
</tr>
<tr>
<td>B2M (ml/min)</td>
<td>0.31 (0.02 – 0.60)</td>
<td>0.04</td>
<td>0.30 (-0.003 – 0.60)</td>
<td>0.05</td>
</tr>
<tr>
<td>Albumin (ml/min)</td>
<td>0.04 (0.006 – 0.06)</td>
<td>0.02</td>
<td>0.04 (0.005 – 0.07)</td>
<td>0.02</td>
</tr>
<tr>
<td>IgG (µl/min)</td>
<td>20.9 (-1.1 – 42.9)</td>
<td>0.06</td>
<td>20.3 (-2.5 – 43.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>A2M (µl/min)</td>
<td>7.9 (-4.9 – 20.7)</td>
<td>0.22</td>
<td>8.6 (-4.8 – 21.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>-0.08 (-0.41 – 0.24)</td>
<td>0.60</td>
<td>-0.06 (-0.40 – 0.28)</td>
<td>0.73</td>
</tr>
<tr>
<td>ELAR (ml/min)</td>
<td>-0.45 (-1.03 – 0.14)</td>
<td>0.13</td>
<td>-0.44 (-1.04 – 0.16)</td>
<td>0.14</td>
</tr>
<tr>
<td>TCUFR (ml/min)</td>
<td>-0.80 (-1.61 – -0.0001)</td>
<td>0.05</td>
<td>-0.81 (-1.63 – 0.02)</td>
<td>0.06</td>
</tr>
<tr>
<td>Free water transport_{0–60min} (ml)</td>
<td>-16.4 (-82.0 – 49.3)</td>
<td>0.62</td>
<td>1.63 (-65.0 – 68.2)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abbreviations: MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate. Linear mixed models were performed with the group without peritonitis as the reference group. *Adjusted for age and diabetes.

Table 4. Peritonitis group stratified by peritonitis severity

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Adjusted* slope difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTAC creatinine (ml/min)</td>
<td>-0.43 (-6.04 – 5.18)</td>
<td>0.87</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>1 (-17 – 19)</td>
<td>1.00</td>
</tr>
<tr>
<td>TCUFR (ml/min)</td>
<td>-0.43 (-2.01 – 1.14)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Abbreviations: MTAC creatinine, mass transfer area coefficient of creatinine; TCUFR, transcapillary ultrafiltration rate. Adjusted linear mixed models were performed. *Adjusted for age and diabetes. Severe peritonitis (n=9) was defined as one or more peritonitis episodes with a leukocyte count >1,090 cells/mm³ on day 3 or >100 cells/mm³ on day 5 of the peritonitis episode compared with a reference group of less severe peritonitis (n=7).
Sensitivity analyses

Sensitivity analyses showed no effect of the time period of patient inclusion, nor of the number of peritonitis episodes (online supplemental material; see appendix 4 in chapter 10 of this thesis), or their severity on the time course of peritoneal transport. The intermediate peritonitis group had a time-course very similar to that in the no peritonitis group. Severe peritonitis episodes showed a similar association to that of mild peritonitis with peritoneal transport, as shown in Table 4.

Figure 3. Scatter plots for individual dialysate IgG concentrations.
Panel A and B: dialysate IgG for patients without peritonitis (panel A) and patients with frequent peritonitis episodes (panel B) at baseline and late in PD treatment. At baseline, the dialysate concentrations of dialysate IgG were significantly (<0.01) lower in the frequent peritonitis group compared with the no peritonitis group. The dots represent individual patients; the lines represent the median and IQR.

Figure 4. SPA parameters for the no peritonitis group and the frequent peritonitis group, at baseline and late in PD treatment. Baseline values were set to 100%. MTAC creatinine (closed circles), glucose absorption (open circles), transcapillary ultrafiltration (TCUFR) (closed squares), and the restriction coefficient (closed triangles) are given. When comparing the slopes of the transport parameters between the no peritonitis and the frequent peritonitis group, frequent peritonitis was associated with the development of a faster small solute transport (MTAC creatinine p = 0.03, glucose absorption p = 0.09) and a concomitant lower TCUFR (p = 0.06). No difference in the rate of change of the restriction coefficient was found (p = 0.73).
Discussion

In the present study we found that patients who experienced frequent episodes of peritonitis during a three years follow-up period had lower peritoneal clearances of serum proteins at the start of PD treatment, compared with patients without peritonitis. A concomitant higher restriction coefficient to these macromolecules in the frequent peritonitis group was found. Peritoneal transport of macromolecules from the circulation to the dialysate is size-selectively restricted by the intrinsic permeability of the peritoneal membrane.\textsuperscript{20,21} As a consequence their mass transfer area coefficients or clearances are determined both by the effective peritoneal surface area (the total number of intercellular pores) and by the intrinsic peritoneal permeability (the large pore radius). The latter can be expressed as the peritoneal restriction coefficient, thus the higher the restriction coefficient, the lower the permeability to macromolecules. Peritoneal mass transfer area coefficients of solutes can be used as an indicator for the effective peritoneal surface area, provided that their transport is not hampered by the intrinsic permeability of the membrane, which is the case for small solutes, including B2M.\textsuperscript{22,23} In the present study, no difference in B2M clearance between the no peritonitis and frequent peritonitis group was found at baseline. However differences were found in the clearances of larger proteins, like albumin, IgG, and A2M, indicating that rather than a lower effective surface area, a lower intrinsic permeability of the peritoneal membrane is the cause of this observation. As a consequence, this led to lower dialysate concentrations of albumin, IgG and A2M.

Evidence suggests that cytokines, such as interleukin-6 (IL-6), growth factors like vascular endothelial growth factor, together with the release of nitric oxide by endothelial cells, play an important role in the regulation of vascular density and permeability within the peritoneum. Zemel \textit{et al.} reported local production of IL-6 within the peritoneal cavity in stable CAPD patients without peritonitis.\textsuperscript{24} Dialysate IL-6 was related to permeability characteristics of the peritoneal membrane, because elevated levels of IL-6 were associated with an increased intrinsic permeability and higher IgG clearances. Pecoits-Filho \textit{et al.} found relationships between dialysate IL-6 and peritoneal albumin clearances.\textsuperscript{25} The possibility of IL-6 as a determinant of differences in peritoneal membrane transport characteristics at the start of PD is further supported by the finding of Gillerot \textit{et al.} who identified the -174G/C polymorphism of IL-6 as an independent predictor of solute transport. In that study dialysate IL-6 concentrations were higher at the start of PD in patients harboring the CC and GC genotypes compared with the GG genotype.\textsuperscript{26} It may be that some patients at the start of PD have low dialysate IL-6 concentrations leading to a decreased large pore size, with decreased permeability of the peritoneal membrane and low dialysate protein levels as a consequence. However, effluent IL-6 concentrations were not available in the present study. In our analysis the frequent peritonitis group was the group with lower dialysate IgG
levels at the start of PD, compared with the no peritonitis group. Others found that baseline values of peritoneal protein leakage, estimated by peritoneal total protein clearance, were independent predictors of peritonitis. However, unlike our study, analysis of individual proteins in PD effluent was not performed and total protein losses were measured in 24-hour effluent. In contrast, Zemel et al. did not find a correlation between dialysate IgG concentration and overall peritonitis incidence, but in this study dialysate IgG was determined at any moment during PD.

It is known that for most pathogens, opsonization is essential for efficient phagocytosis. This is dependent on the concentration of specific IgG and/or alternate pathway complement components. In vitro studies have shown that dialysate IgG is involved in the opsonisation of bacteria. We hypothesize that slow initial peritoneal transport rates of serum proteins result in lower dialysate concentrations of IgG, and likely a lower opsonic activity, which is a risk factor for peritonitis. This is supported by the findings of Lamperi and colleagues. These authors found a significant correlation between the opsonisation capacity for bacteria and IgG concentrations in peritoneal effluent. Moreover, they reported an inverse correlation between the opsonic capacity of effluent and the number of episodes of peritonitis. Intraperitoneal immunoglobulin treatment raised the dialysate opsonisation capacity and lowered peritonitis incidence in patients with a previously high incidence of peritonitis. In another study, these authors demonstrated that for patients in whom the immunoglobulin therapy did not reduce the peritonitis incidence, only transient increases in the dialysate IgG and opsonic activity levels were present. This was due to a defective number of peritoneal macrophages Fc receptors, and consequently, a decreased binding capacity of IgG.

After 3 years of PD, the differences in dialysate concentrations of macromolecules between the no peritonitis group and the frequent peritonitis group were not present anymore. Several studies reported increased dialysate levels of cytokines and eicosanoids during peritonitis, leading to an increase of the effective surface area of the peritoneum, increased protein clearances and a concomitant decreased restriction coefficient. It may be that after several episodes of peritonitis these effects are not only temporary, but also partly sustained, which explains the observation that after three years of PD, the dialysate concentrations of macromolecules are equal between the two groups.

In the present study, patients with frequent peritonitis episodes showed an increase in small solute transport and a decrease of ultrafiltration, which was not found in peritonitis-free patients. The latter group, in which the natural time-course of peritoneal transport is reflected, showed a significant decrease from baseline to late in PD treatment for MTAC creatinine and glucose absorption, accompanied by an increasing trend for transcapillary ultrafiltration. This is in contrast with previous studies showing an increase in small solute transport and glucose absorption with time on PD. Apparently, this does not apply to patients without peritonitis, or patients with only 1 or 2 peritonitis episodes. Therefore, the
Mutual relationship between peritonitis and peritoneal transport

detrimental effects on the time-course of peritoneal transport are only evident in patients with frequent peritonitis episodes. Several studies found no correlation between peritonitis and changes in peritoneal transport,\textsuperscript{41-43} probably due to the short observation time, a sub-optimal assessment of peritoneal function or by inclusion of patients with a limited number of peritonitis episodes. In concordance with our findings, Davies \textit{et al.} showed that frequent peritonitis episodes were associated with significant increases in D/P creatinine and reductions in ultrafiltration volume.\textsuperscript{8} This was also found in a more recent study by Fernández-Reyes and colleagues.\textsuperscript{44} It suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area. Our observation that frequent peritonitis episodes had no significant effect on the time-course of the restriction coefficient to macromolecules suggests that the increase in the effective peritoneal surface area may develop without the concomitant fibrotic structural membrane alterations that may develop after long-term PD. The present study has some limitations. First, the study population represents a selective group of patients. Because PD is associated with a high dropout rate due to technique failure, transplantation or death, 53\% of the original cohort of patients could not be included because of an insufficient follow-up, mainly due to transplantation or death. Obviously, patients with a more severe peritonitis episode were more at risk to be lost to follow-up. However, this selection procedure will lead to the loss of more patients with altered solute transport and ultrafiltration failure, making the observation of this study more clinically relevant. Moreover, there were no differences in patient characteristics between both groups at baseline. In addition, it can be speculated that the lower peritoneal clearance of macromolecules found in the frequent peritonitis group at baseline, is due to informative censoring, as recently pointed out by Yu and colleagues.\textsuperscript{10} These authors refer to studies in which a high protein clearance at baseline is an independent predictor of survival, which may result in the potential confounding of longitudinal data due to earlier dropout of patients with high protein clearances. However, in a larger study with a longer observation period no association between protein clearance and survival was found.\textsuperscript{45} Second, dialysate concentrations of cytokines and growth factors could not be determined, as discussed above. Nevertheless, previous studies clearly demonstrated the role of IL-6 in peritoneal protein transport.\textsuperscript{24,25} Thirdly, in our dialysis unit the type of dialysis solution has been changed over the years. Although we could not analyze possible effects of these changes, the sensitivity analysis comparing the two time periods gives no indication for this. One of the strengths of this study is the use of the Standard Peritoneal permeability Analysis instead of the Peritoneal Equilibration Test (PET), which provides additional information on pathways of fluid transport and includes the peritoneal clearances of several serum proteins from which the restriction coefficient to macromolecules can be calculated.\textsuperscript{46} Moreover, very strict inclusion criteria were used: a SPA within the first year and within the third year of PD had to be available, without peritonitis preceding the first SPA. A group without
peritonitis and a group with frequent peritonitis were formed. Because of this, we were able to distinguish between changes in peritoneal transport due to frequent peritonitis episodes, and changes caused by PD duration itself.

Conclusions

The present study has demonstrated that patients with frequent peritonitis episodes had an increase in small solute transport and a decrease of ultrafiltration, which was not found in patients without peritonitis. This suggests that frequent peritonitis leads to an increase of the vascular peritoneal surface area without all the structural fibrotic membrane alterations that may develop after long-term PD. In addition, compared with patients without peritonitis, patients who experienced frequent episodes of peritonitis had lower peritoneal clearances of serum proteins at the start of PD. These lower clearances result in lower dialysate concentrations of IgG and likely a lower opsonic activity, which is a risk factor for peritonitis.
References


Chapter 9

Summary and general discussion
The research reported in this thesis aimed to contribute to the knowledge about the epidemiology of infectious complications in peritoneal dialysis (PD) patients and its subsequent impact on peritoneal transport characteristics. First, we studied the incidence of infectious complications on dialysis. Second, determinants of infectious complications, in general, and specifically peritonitis were investigated. Finally, the association of peritonitis with peritoneal transport characteristics was analyzed. In this chapter, the main findings of our studies are summarized, highlighted and put in a broader perspective. We elaborate on the implications for clinical practice and provide guidance for future research.

Main findings

In chapter 2 the incidence of all infectious complications in hemodialysis (HD) and PD patients was assessed. This chapter provides evidence that PD patients carry a higher baseline risk for infections when compared with HD patients. A large proportion of the infections in PD patients were related to the PD technique, whereas this was different for HD patients. HD patients developed more infections that were not related to the dialysis technique. We hypothesize that modality-induced immunodeficiency, environmental factors or residual confounding as a consequence of differences in the underlying health status may explain the latter observation.

In chapter 3, the association between protein-energy wasting, an aspect of the underlying health status, and the risk of infections in patients on dialysis was investigated. Protein-energy wasting was associated with a 40% increased risk of infections in both HD and PD patients. The association was not different across strata of dialysis modality. Both the overall subjective global assessment (SGA) classification and the four SGA subscales were associated with the risk of infection. Our study underlines that routine screening of nutritional status with the SGA is important in all dialysis patients.

Peritonitis is the most important infectious complication in PD. In chapter 4 and 5, the association between exit site infection and subsequent peritonitis was studied. Using data from a randomized controlled trial (RCT), we have shown a strong temporal association between a recent exit site infection and the development of subsequent peritonitis. Interestingly, in almost all cases a discrepancy was observed between the organism cultured from the exit site and that grown from the peritoneal effluent. In addition, the aggressiveness of the treatment, systemic versus topical antibiotics, did not alter the risk of subsequent peritonitis.

It can be concluded that the literature provides evidence for a relationship between exit site infection and peritonitis. However, whether this relationship is causal or associative remains uncertain. Therefore, a qualitative assessment of the literature using the Bradford Hill
criteria was performed. Only an association and no causal relationship could be attributed. In PD, the peritoneum and its peritoneal host defense mechanisms are exposed to high concentrations of glucose in the dialysate. However, the results presented in chapter 6 indicate that no association between glucose exposure and the time to subsequent peritonitis is present in PD patients. This suggests that the high concentrations of glucose in the dialysate might not only have detrimental effects on the peritoneal host defense, but also on the function and survival of the invading pathogens. It is likely that the balance between the two determines the risk of peritonitis.

In chapter 7 and 8, the influence of peritonitis on the possible deterioration of peritoneal transport characteristics was investigated. First, the association between the first peritonitis episode and peritoneal transport was studied. Patients with a very first peritonitis episode remained at an initial faster transport state, whereas patients without a first peritonitis episode showed a stabilization of peritoneal transport parameters presented by a slight decrease of the transport status. Second, the impact of frequent peritonitis episodes on peritoneal transport was studied. Patients who survived three years on PD and experienced frequent peritonitis episodes (≥3) showed an increasing trend in small solute transport and a decreasing trend in transcapillary ultrafiltration, whereas the contrary was true in patients without peritonitis or with one or two episodes. In addition, we found that patients who experienced frequent peritonitis episodes had lower peritoneal clearances of IgG at the start of PD when compared with patients without peritonitis. The lower clearances of IgG lead to lower dialysate concentrations, which might result in lower initial opsonic activity. This may have been a risk factor for the development of frequent peritonitis.

Epidemiology of infections on dialysis

Our study results suggest that the underlying susceptibility for infections might be lower in PD patients when compared with HD patients, which was comparable to previous North-American reports. Three aspects of HD clinical practice are hypothesized to explain the increased susceptibility for infections. The first explanation might be that HD is an intermittent treatment and therefore patients are exposed to more oxidative stress, fluid overload and accumulation of uremic toxins than patients on PD. Also, systemic inflammation due to the contact of the blood with an artificial dialysis membrane appears to be more outspoken in HD patients when compared with PD patients. These consequences of treatment with HD might have immunosuppressive effects. Therefore an increased risk of non-dialysis technique related infections could be observed. Notably, the incidence of pneumonia was higher in HD than PD patients, which has been noticed by others as well. In the United States, influenza and pneumococcal vaccinations are part of qualitative care, whereas no
recommendation has been included in the Dutch guidelines. Observational studies\textsuperscript{11-14} have shown an effect of vaccination on the risk of pneumonia, but a RCT has not been performed. Second, the majority of the HD patients are treated in the hospital and this might be a hostile environment in terms of infection risk. Although likely, we did not find more hospital-acquired causative microorganisms in HD patients nor did others. A third explanation might be that residual confounding explains the observed association. The decision to start dialysis with HD or PD is not only based on measured demographic and clinical parameters, but also on the perception of both the doctor and the patient. Even after extensive adjustment for confounders, HD and PD patients might not be comparable in terms of their underlying health status that determines the risk of infections. Protein-energy wasting is an important representative of this underlying health status. Previous consensus statements of the International society of renal nutrition and metabolism (ISRNM) hypothesized that protein-energy wasting is associated with the risk of infectious complications on dialysis.\textsuperscript{15-17} We investigated the association between protein-energy wasting and infection risk in HD and PD patients separately. Our results confirmed the ISRNM hypothesis and showed that protein-energy wasting is an equally important risk factor for infection in both HD and PD patients, although these patients have a different baseline risk for infection. However, whereas protein-energy wasting increased the risk for both dialysis-technique and non-dialysis technique-related infections in HD patients this was not the case for PD patients. In these patients, protein-energy wasting only influenced the risk of dialysis technique-related infections. Furthermore, protein-energy wasting is more prevalent in HD than in PD patients. This could indicate that the prevalence of protein-energy wasting in HD determines the increased susceptibility for non-dialysis technique-related infections in these patients when compared with PD patients.

Exit site infection and peritonitis

We have shown that a previous exit site infection is associated with a highly increased risk of subsequent peritonitis up to 60 days after the exit site infection. Although evidence for a strong relationship between these two infections has been provided throughout the literature, the relation was found to be associative rather than causal. Similar to Lloyd \textit{et al.}\textsuperscript{18} and Szeto and co-workers,\textsuperscript{19-22} we have shown that the microorganism that previously caused the exit site infection was often not the same as the microorganism cultured from the peritoneal effluent when a subsequent peritonitis occurred. The case series of Szeto \textit{et al.} showed that peritonitis episodes caused by \textit{Staphylococcus aureus}\textsuperscript{19} and \textit{Pseudomonas aeruginosa}\textsuperscript{20} and preceded by an exit site infection were most often caused by the same microorganism (±50%). However, other organisms\textsuperscript{21,22} showed a much lower percentage
of consistency. Furthermore, we have shown that the aggressiveness of the treatment, systemic versus topical antibiotics, did not reduce the risk of subsequent peritonitis. This was consistent with the findings of Lloyd et al., who demonstrated an increased risk of peritonitis despite appropriate antibiotic treatment. Although nonsignificant, we observed that exit site infections treated systemically, carried a higher subsequent peritonitis risk than those treated locally. However, this finding might suffer from confounding by indication.

Our findings, amongst those of others, emphasize that exit site infection can be seen as an “indirect hit” that affects local host defense pathways in the already immunocompromised dialysis patient, rather than being a direct cause of peritonitis. As a consequence of the exit site infection, patients may become even more vulnerable to invasion by pathogens into the peritoneal cavity and therefore develop peritonitis. The exact host defense pathways affected by exit site infections are unknown and future research to evaluate the immunological consequences of an exit site infection leading to peritonitis is required to elucidate this hypothesis.

**Glucose exposure and peritonitis**

Glucose exposure during the first year on PD was not associated with the subsequent time to peritonitis in patients. Our findings are consistent with the results demonstrated by previous RCTs that compared a glucose sparing to a non-glucose sparing regimen. However, they are not consistent with a large body of experimental evidence that has previously shown an effect of glucose on peritoneal host defense. Three explanations can be given for this discrepancy. First, experimental studies might not represent the actual situation in the PD patient. Animals used to study this research question had a normal renal function, the concentrations of glucose exposure used were not representative of the exposure in humans and follow-up times might have been unrealistic to be translated to the patient situation. A second explanation could be that very low glucose exposure is already extremely harmful and increased exposure might not increase its impact on peritoneal host defense and, therefore, peritonitis risk. However, a previous animal model with very low glucose exposure showed no functional and morphological changes. Also, we believe that if glucose exposure affects the risk of peritonitis a dose-response relationship would be present. Although unlikely, no studies have been performed to reject the previous hypothesis. Third, the general perspective on the pathophysiology of the effect of glucose on the risk of peritonitis might have been rather one-dimensional. Researchers focussed on the impact of glucose on the peritoneal host defense and discovered negative effects of both glucose itself and the high osmolality on the defense capacity of monocytes, macrophages, neutrophils and mesothelial cells. However, very little is known about
the potential bacteriostatic or bactericidal effects of high concentrations of “sugar” on the pathogens invading the peritoneal cavity. Studies on the potential of honey in the prevention of infections demonstrated bactericidal concentrations and osmolality that are much higher than that reached by dialysis solutions. However, it could well be that intraperitoneal bactericidal or bacteriostatic effects of glucose play an important role in PD. We hypothesize that the high concentrations of glucose in the dialysate might not only have detrimental effects on the peritoneal host defense, but also on the function and survival of the invading pathogens. Therefore, we believe that it is likely that the balance between the two determines the risk of peritonitis in PD patients.

Peritonitis and peritoneal transport alterations

The results of our studies show that peritonitis is associated with the development of peritoneal transport alterations. Already, a very first peritonitis episode caused patients to remain at their initial faster transport status, whereas patients without a first peritonitis episode showed a stabilization of peritoneal transport parameters presented by a “dip” of solute transport status. Others have described this phenomenon as well and attributed the initial faster transport status to the insertion of the catheter or familiarization with the exposure to dialysis solutions. Interference of the first peritonitis episode with the process of epithelial-to-mesenchymal transition (EMT) within the first year on PD might explain our observation. The landmark paper about EMT by Yáñez-Mó et al. showed that peritonitis has the ability to induce or enhance EMT. A cross-sectional study from the same group found no relation between previous mild peritonitis and the existence of EMT. Mesothelial cells that have undergone EMT are a major source of vascular endothelial growth factor (VEGF). VEGF is an important instigator of neo-angiogenesis and determinant of vascular permeability during PD. Therefore both EMT and the presence of VEGF itself have been associated with an increased vascular peritoneal surface area and, consequently, a faster transport status. Taken together, this might explain why interference of a single peritonitis episode with EMT causes patients to remain at a faster peritoneal transport status.

When patients were followed over a period of three years on PD, no difference between the course of peritoneal transport in peritonitis-free patients and those with one or two episodes was observed. However, patients who experienced frequent peritonitis episodes (≥3) demonstrated an increasing trend in small solute transport and a decreasing trend in transcapillary ultrafiltration. Two pathways are thought to potentially explain this observation. First, previous studies suggested that the presence of extremely high lactate concentrations during PD might lead to an increase in the intracellular NADH/NAD⁺ ratio. An increase of this ratio is a manifestation of cellular ischaemia and has been called
Summary and general discussion

Pseudohypoxia. Pseudo hypoxia is an important contributor to the secretion of VEGF, which has been shown to increase with the duration of PD. The synergistic interaction between the above-described interference of peritonitis with EMT and the impact of chronic exposure to pseudohypoxia may therefore explain our findings. The occurrence of frequent peritonitis might facilitate a larger impact of pseudohypoxia on peritoneal transport through the early existence of a larger peritoneal vascular surface area. Apparently, one or two peritonitis episodes are not enough to exert this effect or were less likely to occur during EMT. This is in line with the findings of Fernández-Reyes et al. that suggest that a fast transport status is a reversible condition when peritonitis is avoided during the early dialysis period. A second pathway might be that patients with frequent peritonitis episodes eventually do not recover anymore from the acute changes and proinflammatory status that exist during peritonitis. This might be because either the lag time between the peritonitis episodes is short or because the reversibility has been tired out. Frequent peritonitis therefore facilitates an accumulative impact on the peritoneal vascular surface area and, therefore, on peritoneal membrane function. This hypothesis is supported by the findings of Davies et al. that showed exacerbation of longitudinal changes in peritoneal transport in patients with multiple peritonitis episodes.

In summary, the results of our studies support the presence of a mutual relation between peritonitis and peritoneal transport. After a very first peritonitis episode, patients already remain at a faster transport status during the first year on PD whereas accumulation of peritonitis episodes is required to deteriorate peritoneal transport in patients on long-term PD.

**Peritoneal IgG clearance and peritonitis**

Patients who experienced frequent peritonitis episodes had lower peritoneal clearances of IgG at the start of PD when compared with patients without peritonitis. A restricted intrinsic permeability and therefore a size-selective lower clearance of IgG have been thought to explain the difference. The lower clearances of IgG decrease the dialysate concentrations of this immunoglobulin and can result in lower initial opsonic activity, which may have been a risk factor for the development of frequent peritonitis later on. This hypothesis is supported by a study by Lamperi et al. who demonstrated an inverse correlation between the opsonic capacity of IgG in the peritoneal effluent and the number of episodes of peritonitis. The authors subsequently treated patients with a high incidence of peritonitis with intraperitoneal immunoglobulins and showed a decrease in their peritonitis incidence. Only patients who were able to increase the dialysate IgG and therefore the opsonization capacity benefitted from intraperitoneal IgG treatment. Intravenous immunoglobulin treatment did not decrease their incidence of peritonitis episodes.
Previous studies with the objective to optimize the dialysis dose investigated both intraperitoneal and oral pharmacological agents to increase peritoneal transport. However, a limited number of these studies determined peritoneal protein clearances and specified the clearance of IgG. Already in the eighties, Nolph and colleagues demonstrated that intraperitoneal nitroprusside increased peritoneal clearances of large solutes.\textsuperscript{53} Douma et al.\textsuperscript{54} investigated the possible role of intraperitoneal administration of nitroprusside in the regulation of the permeability of the peritoneum. They showed a significantly greater clearance of IgG after exposure to nitroprusside. The increased clearance has been explained as a consequence of the vasodilatating effect of nitroprusside, which has led to increased radii of the venular interendothelial gaps (large pores) and therefore less restriction to the clearance of macromolecules. Similar results were found by Tan et al. who showed a higher concentration of IgG in the dialysate in patients treated with nitroprusside.\textsuperscript{55} Rojas-Campos et al.\textsuperscript{56} showed a nonsignificant trend towards increased total protein loss in the dialysate with oral administration of the calcium channel blocker verapamil. However, this was only seen in fast transporters and the amount of IgG was not determined. None of the previous studies was designed to establish the risk of peritonitis after an increase of the amount of IgG in the peritoneal cavity. Therefore, future studies should evaluate the administration of intraperitoneal IgG, intraperitoneal or oral pharmacological agents in a randomized fashion in incident PD patients to assess whether dialysate IgG can diminish the risk of peritonitis.

**Methodological issues**

*Interpretation of observational studies*

Unlike randomized controlled experiments, in observational studies the participation into the study has no influence on the assignment of patients to a certain treatment strategy or clinical condition. In the ideal situation, the study groups only differ in the presence or absence of the exposure and are therefore exchangeable. Therefore, researchers consider the effect of a drug to be causal when a significant result was observed in a RCT. However, a RCT is not always feasible, ethical or financeable. Furthermore, the generalizability can be limited due to the inclusion of relatively healthy and compliant subjects. An observational study can include a representative sample of the population of interest. However, most likely, the groups in an observational study are different in other aspects than the exposure. Therefore, adjustment for confounding should be considered carefully. Causal interpretation of the results of an observational study should be drawn with caution, because unknown or unmeasured confounders might still influence the estimate. However, when a strong effect remains after extensive adjustment for confounding and the potential influence of bias can be ruled out, causal interpretation is not inconceivable. The following paragraphs
Summary and general discussion

will cover the potential influence of confounding, information bias and selection bias in the observational studies conducted in this thesis. In addition, the Bradford Hill criteria will be evaluated.

**Confounding**

To deal with confounding, each analysis in this thesis has been adjusted for known and available confounding variables. In principle, a potential confounder can be identified as a variable that is associated with the exposure, is a determinant of the outcome and is not within the causal pathway of the association of interest. In chapter 2 extensive adjustments were made for age, sex, diabetes, body mass index (BMI), Kahn comorbidity score, primary kidney disease, ethnicity, malignancy, chronic pulmonary disease, educational level, smoking and dialysis preparation in an outpatient setting. The analyses in chapter 3 were adjusted for age, Kahn comorbidity-score, sex, primary kidney disease, ethnicity and smoking. Additional adjustments were made in the time-dependent analyses to decrease the possibility that the outcome preceded and caused the exposure instead of the other way around. However, since these adjustments might potentially be in the causal pathway, the analyses were repeated without these adjustment and yielded similar results. Limited adjustments were made in chapter 4, because the number of events was relatively small. Analyses were adjusted for age, sex and diabetes since these variables are considered to be the most certain and important confounding factors. The analyses in chapter 6 were adjusted for age, sex, primary kidney disease, diabetes, Davies comorbidity score and the period effect. It can be argued whether adjustments for CAPD/APD and residual renal function should be made and therefore sensitivity analyses including these variables were performed. The analyses in chapter 7 were adjusted for age, sex and diabetes, whereas in chapter 8 these adjustments were limited to age and diabetes because of the low number of patients included in the study.

Although unlikely, it can be argued whether residual confounding from unmeasured, imperfectly measured, unmeasurable or unknown confounders may still play an important role in the observational studies described in this thesis. Because maximal efforts were made to adjust for known confounding, we believe that it is unlikely that residual confounding completely explains the observations.

**Information bias**

Information bias results from systematic deviation from the true observation and may be a consequence of misclassification of the exposure or the outcome. For the studies conducted in chapter 2, 3, and 6 a retrospective review of medical records was performed. Retrospective studies are, generally more than prospective studies, dependent on accurate records keeping and storage. Information about the exposure or the outcome can therefore
be missing, inaccurate or incorrect and this may lead to misclassification of the patient. When the misclassification of the outcome is independent of the exposure status and vice versa, it will generally lead to a dilution of the effect estimate towards the null value. However, when misclassification of a certain exposure depends on the prognosis of the patient or when misclassification of the outcome is associated with the underlying exposure status, the estimate can both be an under- and an overestimation of the effect. In the latter situation, the misclassification is called “differential” and the direction of the bias and its effect on the estimator are much more difficult to predict.

The quality of our retrospective data collection in chapter 2 and 3 was ascertained by a number of strategies. First, prespecified criteria for the scoring of an infection were developed to maximize intra-observer reproducibility and inter-observer reliability. The methodology used by previous research was reviewed and multiple expert opinions were collected. After the development of the criteria, two reviewers worked in close collaboration to assure similar application of these criteria. Unfortunately, no data was collected about the agreement between the reviewers. Second, we made sure that we conducted a thorough review of both in- and outpatient medical records. As a consequence, we scored all infections under the care of a nephrologist, even if the patient had not been hospitalized. Despite our efforts, infections of less severity may have been underreported, because they were not recorded or were treated by the general practitioner instead of the nephrologist. The adjudication of the day-to-day dialysis schemes for the study described in chapter 6 was conducted according to a similar strategy. PD nurses and staff were interviewed to make sure that all the important information to calculate the exposure to glucose was collected during the review process. All in- and outpatient medical records were reviewed to ascertain that all available information about the dialysis schemes was captured. Misclassification could still result from limited information about the day-to-day dialysis schemes. However, we believe that the relation between day-to-day availability of the information and a patients’ prognosis is limited and therefore non-differential.

The studies described in chapter 4, 7, and 8 were conducted as part of prospective data collections, which might limit information bias but does not essentially mean that information bias is inconceivable. The data in chapter 4 were collected as part of a randomized controlled trial. We cannot exclude that the diagnosis of an exit site infection increases the alertness for a peritonitis episode among both patients and health care practitioners, which might have facilitated the association between exit site infection and peritonitis differentially. All patients in chapter 7 and 8 have complete peritoneal transport data. The availability of peritoneal transport data does not increase the alertness for a peritonitis episode, which excludes differential misclassification.
Selection bias

Selection bias is a systematic error that is a consequence of the design of the recruitment procedures and reasons for participation in the study. Selection bias is present when the association between exposure and outcome is different in the patients participating in the study compared with those who were not approached or not willing to participate in the study. The data used in chapter 4 was collected as part of a randomized controlled trial (RCT). Patients participating in RCT are in general somewhat healthier and more interested in their health and health-related factors. This could result in a study population with a relatively better prognosis than those not included in the study. Indeed, the incidence of infections was fairly low in our study, but this does not influence the internal validity of our study results. However, the external validity might be affected, which means that the strength of the association between exit site infection and peritonitis might be different in a population with a higher incidence of infections. The research described in chapter 7 and 8 was subject to eligibility criteria that excluded a large proportion of patients. This was mainly due to missed assessments of peritoneal transport status. This may have resulted in a selected patient population that was able and willing to come to the hospital for the assessment. Also, patients with peritonitis need to survive peritonitis and remain on PD. We believe that a relatively healthy study population was included in both the (frequent) peritonitis and control group. Therefore, again, the internal validity of the study was not affected, but the external validity might be limited to the somewhat healthier PD patients.

The patient population studied in chapter 6 did not include patients who suffered from an early peritonitis episode or did not survive the first year. This ascertained the internal validity of the study, but resulted in a somewhat limited external validity of the results. The research in chapter 2 and 3 was performed using data from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study. This study was conducted in the majority of the dialysis centers in the Netherlands (38 out of 50). Only a few inclusion criteria were applied: patients needed to be 18 years or older, Dutch-speaking and started their first renal replacement therapy in a clinically stable condition. In this respect, the NECOSAD study was similar to the Dutch end-stage renal disease population included in the data from the Dutch renal replacement registry. For our NECOSAD substudy, we selected three regional hospitals and two university hospitals for reasons of efficient data collection (trade off between the number of included patients and travel distance). When we compared the patient sample from these hospitals to the total NECOSAD population no difference in baseline characteristics was observed. It should be considered that infection rates in both HD and PD patients have declined since the NECOSAD study initiation due to the implementation of preventative measures in clinical practice and therefore the observed number of infections might be somewhat higher than would be expected today. Taken together, we believe that selection bias is very limited in the NECOSAD study and are
therefore confident that the results of our study can be generalized to a Caucasian European adult dialysis population.

**Bradford Hill’s viewpoints for causation**

The British Epidemiologist Sir Austin Bradford Hill (1897-1991) developed a list of nine conditions necessary to support a causal relationship between an exposure and its outcome. Hill's intention was to provide guidelines for interpretation, rather than criteria to be used as a checklist. Furthermore, Hill postulated that none of the described conditions could serve as indisputable evidence for or against a causal relationship. However, ironically, Hill’s paper became famous for its “criteria” to separate causality from non-causal associations. Consequently, over the years, the application of the Hill’s criteria for the assessment of (causal) relationships has led to much debate. Howick et al. preferred to restructure Hill’s viewpoints into 3 main categories: direct evidence, mechanistic evidence and parallel evidence and emphasized the usefulness of these revised criteria to evaluate causality. Rothman and Greenland underlined that the viewpoints of Hill should be used as an intellectual exercise rather than to refute or ascertain a causal relation. Philips and Goodman stated that Hill's considerations are under-appreciated as “guideposts on the road to common sense”, whereas Ward believed that there is an important role for the Hill’s criteria in the justification of further research. Taken together, epidemiologists acknowledge the value of the Hill’s considerations in the evaluation of the available evidence, but reject that satisfaction of the nine viewpoints is required to establish a degree of causality. However, many researchers have used the Hill’s “criteria” for causation to evaluate the evidence available in their field. We used the Bradford Hill criteria in chapter 5 for guidance of causal inference. Our approach was similar to that of many others researchers which indicates that we explained per criterion why it was or was not fulfilled and drew conclusions from this information. One of the difficulties of this approach is that Hill did not specify the weight of the criteria. Also, it is almost impossible to fulfill a criterion with 100% certainty. Therefore, the overall assessment of the available evidence could suffer from limited transparency, reproducibility and subjectivity. Although, causal inference from observational studies might be seen as a subjective process in principal, transparency and reproducibility should be improved to ascertain its validity. By the use of quality criteria for inclusion in the review and an extensive description of the assessment of the studies we aimed to maximize the transparency and reproducibility of the research described in chapter 5. However, Swaen et al. attempted to weight the Bradford Hill criteria and developed a method to estimate the likelihood of the presence of causality. Although, their approach is transparent and reproducible, it is still not objective. However, the interesting component of their approach is the calculation of a non-dichotomous outcome. This probabilistic approach complements the debate in the literature in a way that it allows evaluation of cause-effect relations but leaves room for doubt about causality.
Recommendations for clinical practice

During the counselling for dialysis, attention should be paid to dialysis modality related infection risk and accompanying preventative strategies. Once dialysis has been started, routine screening of nutritional status is important in every dialysis patient. Furthermore, center-tailored preventative strategies to reduce the risk of exit site infections in PD should be implemented in clinical practice to prevent peritonitis. Treatment of exit site infections should be evaluated critically and monitored intensively to obtain the best results according to the microbiological profile cultured. Although the incidence of peritonitis has decreased over the years, its prevention remains essential to avoid a faster peritoneal transport status.

Recommendations for future research

- In order to provide evidence that the initiation of HD or PD is associated with the underlying susceptibility for infections, in principal, a RCT is necessary. However, previous efforts to perform a RCT comparing HD and PD patients failed and provided convincing evidence that this is very unlikely to be successful in the future. Therefore, an observational study that includes patients on predialysis who are followed on dialysis is the best study design to answer this question. Nowadays such a study is conducted in Europe, including The Netherlands, namely the EQUAL study. The investigation of clinical factors as well as laboratory parameters and DNA could provide better insight into the pathways underlying the infection risk in dialysis patients.

- A RCT would be the most desirable design to proof the effectiveness of pneumococcal vaccination for the prevention of pneumonia in dialysis patients.

- Future studies are needed to entangle the influence of protein-energy wasting, uremic immunodeficiency and the catabolic characteristics of the dialysis procedure itself on the risk of infections. Intervention studies focussing on the improvement of the nutritional status and muscle mass are needed to establish whether a decrease of infection risk can be achieved by an improvement of the body composition of dialysis patients.

- A risk factor such as SGA can be investigated from two epidemiologic perspectives: 1) investigation of the SGA as a screening tool for prediction of outcomes and 2) investigation of the SGA as an etiologic risk factor, which can be intervened on. We studied SGA from the latter perspective. However, research to determine whether SGA would add predictive value to a prediction model for outcomes such as infection could be important to further evaluate its potential purposes as a predictor in clinical practice.
• The recent ISPD guidelines for research into catheter-related infections should be adopted. Manu-
scripts reporting on the association between exit site infection and peritonitis should include a clear definition of these infections, a time interval between them, support the results with a numeric estimate of the risk strength, and distinguish between exit site infection and tunnel infection if possible.

• PD physicians might reconsider the assumption that exit site infection leads directly to subsequent peritonitis. Future research is necessary to investigate the influence of an exit site infection on local defense mechanisms that should prohibit the entrance of pathogens along the catheter tract. Also, the nature of patient-related contributing factors should be investigated.

• A novel method to quantify glucose exposure in PD patients, as proposed in this thesis, should be used in studies investigating the implications of the glucose load.

• A randomized controlled trial in PD patients to study the effect of intraperitoneal application of IgG on the risk of peritonitis is needed to evaluate its potential in clinical practice.

• Large PD patient cohorts with routine assessment of peritoneal transport are very helpful to gain better understanding of the peritoneal membrane and peritoneal transport in general. This may contribute to future improvements of PD therapy.
References


Summary and general discussion


61. Philips CV, Goodman KJ. Causal criteria and counterfactuals; nothing more (or less) than scientific common sense. *Emerg Themes Epidemiol* 2006; 3: 5.


Chapter 10

Dutch summary/Nederlandse samenvatting
Dit proefschrift beschrijft epidemiologisch onderzoek naar het voorkomen van, risicofactoren voor en gevolgen van infecties bij peritoneale dialyse (PD) patiënten. In dit hoofdstuk worden de onderzoeksresultaten samengevat in de Nederlandse taal.

Samenvatting van de belangrijkste bevindingen

In hoofdstuk 1 wordt het onderzoek in dit proefschrift geïntroduceerd. De geschiedenis en epidemiologie van PD worden beschreven, mogelijke risicofactoren voor infecties uiteengezet en de principes van peritoneaal transport toegelicht. Tevens worden de onderzoekscohorten beschreven en de doelstellingen per hoofdstuk uiteengezet. In hoofdstuk 2 wordt het voorkomen van infecties op PD en hemodialyse (HD) beschreven en met elkaar vergeleken. Hieruit is gebleken dat PD patiënten een hoger risico hebben op het ontwikkelen van infecties dan HD patiënten. PD patiënten ontwikkelen met name infecties die te relateren zijn aan de dialysetechniek, terwijl dit bij HD patiënten niet het geval is. HD patiënten ontwikkelen juist meer infecties die niet te relateren zijn aan de dialysetechniek dan PD patiënten. HD patiënten lijken hierdoor kwetsbaarder voor infecties te zijn. We denken dat deze bevinding verklaard kan worden door dialysemodaliteit geïnduceerde immuundeficiëntie, omgevingsfactoren of residuale confounding gerelateerd aan de onderliggende gezondheidstoestand van de patiënt. In hoofdstuk 3 wordt een aspect van deze gezondheidstoestand onderzocht: de associatie tussen protein-energy wasting ("eiwit- en energieverlies") en het risico op infecties bij patiënten op dialyse. Protein-energy wasting was geassocieerd met een 40% verhoogd risico op infecties bij zowel HD als PD patiënten. Alle componenten van protein-energy wasting (gewichtsverlies, gastro-intestinale symptomen, vetverlies en spierverlies) waren geassocieerd met infectierisico. In PD patiënten viel op dat een slechtere voedingsstatus niet geassocieerd is met het risico op niet-dialyse techniek-gerateerde infecties terwijl dit bij HD patiënten wel het geval was. Onze studie benadrukt het belang van routinematig screenen van de voedingsstatus bij alle dialyse patiënten. Daarnaast is het belangrijk dat zowel voedingsinterventies als bewegingsinterventies worden onderzocht op hun effect op uitkomsten zoals het risico op infecties. Peritonitis, of buikvliesonteking, is de meest voorkomende infectie bij patiënten die behandeld worden met PD. In hoofdstuk 4 en hoofdstuk 5 wordt de associatie tussen huidpoortinfecties en het hierop volgende risico op peritonitis bestudeerd. Voor het onderzoek in hoofdstuk 4 werden de gegevens van een Canadees gerandomiseerd gecontroleerd onderzoek (RCT) gebruikt. Een recente huidpoortinfectie is sterk geassocieerd met het risico op hierop volgende peritonitis. Opvallend is dat in bijna alle gevallen (op 1 na) het organisme dat de huidpoortinfectie veroorzaakte niet hetzelfde organisme was als die gekweekt werd uit het peritonitis dialysaat. Daarnaast lijkt systemische of lokale behandeling van de
huidpoortinfectie geen invloed te hebben op het risico op peritonitis. Er bestaat veel literatuur die een relatie tussen huidpoortinfecties en peritonitis ondersteunt. Echter, of dit een causale relatie is of slechts een associatie, is onduidelijk. Daarom wordt in hoofdstuk 5 een literatuuronderzoek beschreven waarbij de Bradford Hill criteria³ werden gebruikt om te beoordelen of de literatuur kwalitatief in staat is om een causale relatie te onderbouwen. Echter, er blijkt onvoldoende ondersteuning te zijn voor een causal verband en daarom concluderen wij dat er sterk wetenschappelijk bewijs is voor een associatie tussen huidpoortinfecties en peritonitis, maar niet voor een direct causaal verband.

Het peritoneum, of het buikvlies, van patiënten die behandeld worden met PD wordt blootgesteld aan hoge concentraties glucose in de dialysevloeistof. Ook de peritoneale verdedigingsmechanismen worden hiermee belast en mogelijk door aangetast. Echter, de resultaten in hoofdstuk 6 laten zien dat er geen associatie bestaat tussen de blootstelling aan glucose en het risico op peritonitis in PD patiënten. Dit suggereert dat hoge glucoseconcentraties in het dialysaat niet alleen schadelijk effecten sorteren op de peritoneale verdedigingsmechanismen, maar mogelijk ook op de pathogenen die de buikholte hebben weten te bereiken. Het is waarschijnlijk de balans hiertussen het risico op peritonitis bepaalt.

In hoofdstuk 7 en hoofdstuk 8 wordt de invloed van peritonitis op veranderingen in het peritoneale transport onderzocht. Allereerst wordt in hoofdstuk 7 het effect van de eerste peritonitis episode op peritoneaal transport bestudeerd. Patiënten met een eerste peritonitis behouden een snellere transportstatus, terwijl patiënten zonder deze eerste peritonitis een lichte daling of stabilisatie van de transportstatus laten zien. Daarnaast wordt in hoofdstuk 8 de impact van frequentie peritonitis episodes op peritoneaal transport onderzocht. Patiënten die drie jaar behandeld worden met PD en frequent peritonitis ontwikkelden (≥3) hebben een stijgend klein moleculair transport en een dalende transcapillaire ultrafiltratie, terwijl het tegenovergestelde wordt geobserveerd in patiënten zonder peritonitis of met 1 of 2 episodes. Opvallend was dat patiënten die uiteindelijk frequente peritonitis ontwikkelden, bij de start van dialyse een lagere peritoneale klaring van immunoglobuline G (IgG) hadden in vergelijking met patiënten zonder peritonitis. De lagere klaring van IgG leidt tot lagere dialysaattconcentraties van IgG, die zouden kunnen leiden tot een lagere opsonische activiteit. Dit zou een risicofactor voor het ontwikkelen van frequentie peritonitis kunnen zijn geweest.

**Implicaties voor de klinische praktijk**

Tijdens de training voor dialyse moet aandacht worden besteed aan het infectierisico en de bijbehorende preventieve maatregelen die gerelateerd zijn aan de keuze voor
een dialysemodaliteit. Na de start van de dialyse is het belangrijk om bij iedere dialyse patiënt routinematig de voedingsstatus te beoordelen. Daarnaast, moeten centrum-toegespitste preventieve strategieën om het risico op een huidpoortinfectie te verkleinen geïmplementeerd worden in de klinische praktijk om peritonitis te voorkomen. De behandeling van huidpoortinfecties moet kritisch gemonitord en geëvalueerd worden zodat de beste behandelresultaten kunnen worden behaald bij het microbiologische profiel. Alhoewel de incidentie van peritonitis de afgelopen jaren gedaald is, blijft de preventie van deze infectie essentieel om de ontwikkeling van een snellere peritoneale transport status uit te stellen.

Aanbevelingen voor nader onderzoek

- Om te bewijzen dat dialysemodaliteit geassocieerd is met een bepaalde onderliggende gevoeligheid voor infecties is in principe een RCT noodzakelijk. Echter, in het verleden hebben inspanningen om een RCT uit te voeren waarin HD en PD patiënten met elkaar vergeleken werden gefaald en ons bovendien overtuigd dat de kans heel klein is dat dit in de toekomst wel succesvol zal zijn. De beste studieopzet om deze vraag te onderzoeken is daarom een observationele studie waarin patiënten vanaf predialyse worden vervolgd op dialyse. Vandaag de dag wordt een dergelijke studie uitgevoerd in Europa, waaronder Nederland, onder de naam EQUAL studie. Onderzoek naar klinische factoren alsmede laboratorium parameters en DNA kunnen mogelijk meer inzicht verschaffen in de onderliggende pathofysiologie van het infectie risico bij dialyse patiënten.

- De effectiviteit van pneumokokken vaccinatie om longontsteking te voorkomen zou moeten worden onderzocht in een RCT.

- Nader onderzoek is nodig naar de invloed van protein-energy wasting, uremische immuundeficiëntie en katabole effecten van de dialyse procedure op het risico op infecties. Interventiestudies gericht op de verbetering van de voedingsstatus of de spiermassa moeten gaan aantonen of een verbetering van deze parameters ook daadwerkelijk leidt tot een verlaging van het risico op infecties bij dialyse patiënten.

- Een risicofactor zoals de voedingstoestand, gemeten met de “subjective global assessment” (SGA) kan worden bestudeerd vanuit twee epidemiologische perspectieven: 1) Het onderzoek naar de SGA als onderdeel van een screeningsmethode om de prognose van de patiënt te voorspellen 2) Het onderzoek naar de SGA als een etiologische risicofactor waarop geïnterveneerd kan worden. Het onderzoek beschreven in dit proefschrift is uitgevoerd vanuit het tweede perspectief. Echter, onderzoek naar de toegevoegde prognostische
waarde van de SGA in een predictiemodel voor uitkomsten zoals infectierisico zou waardevol kunnen zijn om de potentiele klinische waarde van de SGA als predictor te verkennen.

- De meest recente ISPD (International Society for Peritoneal Dialysis) richtlijnen voor onderzoek naar katheter-gerelateerde infecties moeten worden geadopteerd. Wanneer de associatie tussen huidpoortinfecties en peritonitis wordt bestudeerd moeten duidelijke definities voor deze infecties worden gebruikt, het tijdsinterval tussen de infecties worden vastgelegd, een effectschatter worden berekend, en tevens het onderscheid tussen huidpoort- en tunnelinfecties worden gemaakt.

- De aannemer dat huidpoortinfecties een directe oorzaak zijn van hierop volgende peritonitis zou heroverwogen kunnen worden door nefrologen. Nader onderzoek zal moeten bestuderen wat de invloed is van huidpoortinfecties op de lokale verdedigingsmechanismen die de toegang voor pathogenen tot de buikholte zouden moeten versperren. Daarnaast zouden patiënt-gerelateerde factoren die bijdragen aan de onderdrukking van deze verdediging, nader onderzocht moeten worden.

- De nieuwe methode om glucose blootstelling bij PD patiënten te berekenen, zoals beschreven in dit proefschrift, zou gebruikt kunnen worden in studies die de invloed van glucose blootstelling onderzoeken.

- Om het effect van intraperitoneale toediening van IgG op het risico op peritonitis te onderzoeken in de hedendaagse PD populatie en de implicaties voor de klinische praktijk te definiëren is een RCT onder incidente PD patiënten nodig.

- Grote cohorten met incidente PD patiënten waarin routinematig het peritoneaal transport met een gestandaardiseerde methode wordt gemeten zijn erg belangrijk om kennis te vergaren over het peritoneaal membraan en peritoneaal transport. Deze kennis kan bijdragen aan de verbetering van de PD behandeling in de toekomst.
Referenties


Chapter 11

Appendices
Appendix 1: chapter 1

Supplemental figure: detailed age-standardized infection incidence per dialysis year over time

Time in months after the start of renal replacement therapy.

Infection Incidence per Dialysis Year
Appendix 2: chapter 2

Dutch Subjective global assessment score form:

Deel A: Anamnese

_Gewichtsverandering_
Totale verandering over de afgelopen 6 maanden: _____ kg
Percentage verandering:
☐ Toename of <5% afname
☐ 5%-10% afname
☐ >10% afname

Verandering over de afgelopen 2 weken:
☐ Toename
☐ Geen verandering
☐ Afname

<table>
<thead>
<tr>
<th>SGA Score Gewichtsverandering</th>
<th>Ernstig ondervoed</th>
<th>Matig-licht ondervoed</th>
<th>Normaal gevoed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

_Voedselinname_
Huidige voeding
☐ Adequate inname
☐ Inadequate inname

Aandachtspunten voedingsinname
☐ Weinig vast voedsel
☐ Vloeibaar
☐ Voedingssupplementen
☐ Bijna niets

Duur: _____ weken

_Gastro intestinale symptomen_
☐ Gebrek aan eetlust
☐ Misselijkheid
☐ Braken
☐ Diarree

<table>
<thead>
<tr>
<th>SGA Score Voedselinname en Gastro Intestinale symptomen</th>
<th>Ernstig ondervoed</th>
<th>Matig-licht ondervoed</th>
<th>Normaal gevoed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Duur: _____ weken

Deel B: Lichamelijk onderzoek

Teken van:

_Afname onderhuids vetweefsel_

_Spieratrofie_

<table>
<thead>
<tr>
<th>SGA Score Lichamelijk onderzoek</th>
<th>Ernstig ondervoed</th>
<th>Matig-licht ondervoed</th>
<th>Normaal gevoed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Deel C: SGA Classificatie

<table>
<thead>
<tr>
<th>SGA Score Classificatie</th>
<th>Ernstig ondervoed</th>
<th>Matig-licht ondervoed</th>
<th>Normaal gevoed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3: chapter 6

Appendix: glucose exposure graph with consecutive examples to illustrate the quantification method

Examples:

1. Patient A, treated with CAPD, has a dialysis scheme of 3 * 2 liters 2.27% glucose by day and 1 * 2 liters icodextrin overnight. The geometric mean glucose exposure in mmol/L during the dwell can be depicted from the graph in appendix 1. The graph provides that a four-hour dwell (x=2 in graph) with 2.27% glucose results in 74 mmol/L glucose exposure during the dwell. The glucose exposure values per dwell can be multiplied by the dwell time fraction per 24 hours: (74 * (4/24)) + (74 * (4/24)) + (74 * (4/24)) + (0 * 8/24) = 37.0 mmol/L during 24 hours.

2. Patient B, treated with APD, has a dialysis scheme with a total duration of 8 hours consisting of 5 cycli of 1.5 liters of which 3 with 1.36% glucose and 2 with 2.27% glucose and a last bag of 1.5 liters icodextrin. The geometric glucose exposure in mmol/L during the dwell can be depicted from the graph in appendix 1. The graph provides that a 1.6-hour dwell (x=0.8) with 1.36% glucose results in 59 mmol/L glucose exposure during the dwell. The graph provides that a 1.6-hour dwell (x=0.8) with 2.27% glucose results in 98 mmol/L glucose exposure during the dwell. The glucose exposure values per dwell can be multiplied by the dwell time fraction per 24 hours: (59 * (1.6/24)) + (59 * (1.6/24)) + (59 * (1.6/24)) + (98 * (1.6/24)) + (98 * (1.6/24)) + (0 * 1.6/24) = 24.9 mmol/L during 24 hours.

3. Patient C was treated with the CAPD dialysis scheme of Patient A during 3 months (91 days), treated with the APD rinsing scheme of Patient B during the following 1 month (30.3 days) and switched back to the previous CAPD scheme during the next 2 months (60.7 days). To quantify the glucose exposure during these 6 months of PD the following calculation can be made: {(37.0 * 91) + (24.9 * 30.3) + (37.0 * 60.7)} / 182 = 34.99 mmol/L during 24 hours.
3. Patient C was treated with the CAPD dialysis scheme of Patient A during 3 months (91 days), treated with the APD rinsing scheme of Patient B during the following 1 month (30.3 days) and switched back to the previous CAPD scheme during the next 2 months (60.7 days). To quantitate the glucose exposure during these 6 months of PD the following calculation can be made: \( \frac{(37.0 \times 91) + (24.9 \times 30.3) + (37.0 \times 60.7)}{182} = 34.99 \text{ mmol/L during 24 hours.} \)
### Supplemental Table 1: Baseline characteristics of the three groups: no peritonitis, intermediate (1-2 episodes of peritonitis) en frequent (≥3 peritonitis episodes)

<table>
<thead>
<tr>
<th></th>
<th>No peritonitis</th>
<th>Intermediate peritonitis</th>
<th>Frequent peritonitis</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>28</td>
<td>23</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>14:14</td>
<td>16:7</td>
<td>10:6</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean age (yrs) at start PD</td>
<td>55 ± 14</td>
<td>51 ± 15</td>
<td>50 ± 14</td>
<td>0.53</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of ESRD</td>
<td></td>
<td></td>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td>Renal vascular disease</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>9</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>9</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Davies comorbidity score (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>0 comorbidities</td>
<td>29</td>
<td>35</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>1-2 comorbidities</td>
<td>54</td>
<td>52</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>≥ 3 comorbidities</td>
<td>18</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Treatment modality (APD:CAPD)</td>
<td>6:12</td>
<td>5:18</td>
<td>5:11</td>
<td>0.73</td>
</tr>
<tr>
<td>Residual renal function estimated by serum b2-microglobuline at baseline (mg/L)</td>
<td>19.4 ± 8.2</td>
<td>22.8 ± 8.7</td>
<td>23.8 ± 7.9</td>
<td>0.08</td>
</tr>
<tr>
<td>Time from start PD to baseline SPA in months (median (IQR))</td>
<td>5 (4-6)</td>
<td>5 (4-6)</td>
<td>4 (3-6)</td>
<td>0.25</td>
</tr>
<tr>
<td>Time from start PD to late SPA in months (median (IQR))</td>
<td>39 (32-41)</td>
<td>36 (33-40)</td>
<td>39 (33-41)</td>
<td>0.84</td>
</tr>
<tr>
<td>Time between baseline and late SPA (median (IQR))</td>
<td>35 (26-36)</td>
<td>33 (28-36)</td>
<td>36 (27-37)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; CAPD, Continuous ambulatory peritoneal dialysis; APD, Automated peritoneal dialysis.
Supplemental Table 2: Comparison of baseline clearances of macromolecules, restriction coefficient and dialysate IgG between the group without peritonitis, the group with intermediate peritonitis episodes and the group with frequent peritonitis episodes.

<table>
<thead>
<tr>
<th></th>
<th>No peritonitis</th>
<th>Baseline SPA intermediate peritonitis</th>
<th>Frequent peritonitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Clearance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B2m (ml/min)</td>
<td>1.2 ± 0.5</td>
<td>1.4 ± 0.6</td>
<td>1.0 ± 0.4</td>
</tr>
<tr>
<td>Albumin (ml/min)</td>
<td>0.11 ± 0.05</td>
<td>0.11 ± 0.06</td>
<td>0.07 ± 0.03*</td>
</tr>
<tr>
<td>IgG (µl/min)</td>
<td>59 ± 30</td>
<td>72 ± 51</td>
<td>36 ± 16*</td>
</tr>
<tr>
<td>A2m (µl/min)</td>
<td>23 ± 20</td>
<td>26 ± 23</td>
<td>11 ± 7*</td>
</tr>
<tr>
<td>Restriction coefficient</td>
<td>2.39 ± 0.32</td>
<td>2.49 ± 0.40</td>
<td>2.64 ± 0.34*</td>
</tr>
<tr>
<td>Dialysate IgG (mg/L)</td>
<td>75.8 ± 42.4</td>
<td>57.7 ± 36.8</td>
<td>45.2 ± 52.4*</td>
</tr>
</tbody>
</table>

Abbreviations: MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate; *Significantly different (p<0.05) between no peritonitis and frequent peritonitis group, and the intermediate and frequent peritonitis group. #Significantly different (p<0.05) between no peritonitis and frequent peritonitis group.

Supplemental Table 3: The adjusted slope differences between the frequent peritonitis group and the no peritonitis group

<table>
<thead>
<tr>
<th>SPA measurement</th>
<th>Time period of PD 1990-2000 (no peritonitis, n=14, frequent peritonitis, n=10)</th>
<th>Time period of PD 2000-2010 (no peritonitis, n=14, frequent peritonitis, n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted* slope difference (95% CI)</td>
<td>Adjusted* slope difference (95% CI)</td>
</tr>
<tr>
<td></td>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>MTAC creatinine (ml/min)</td>
<td>3.38 (-1.16 – 7.91)</td>
<td>2.19 (-1.84 – 6.23)</td>
</tr>
<tr>
<td>Glucose absorption (%)</td>
<td>0.06 (-0.05 – 0.18)</td>
<td>0.07 (-0.04 – 0.17)</td>
</tr>
<tr>
<td>TCUFR (ml/min)</td>
<td>-0.10 (-2.23 – 0.25)</td>
<td>0.04 (-1.50 – 1.58)</td>
</tr>
</tbody>
</table>

Abbreviations: MTAC creatinine, mass transfer area coefficient of creatinine; ELAR, effective lymphatic absorption rate; TCUFR, transcapillary ultrafiltration rate.*Adjusted for age, sex and diabetes.
Supplemental figure 1. SPA parameters for the intermediate peritonitis group, at baseline and late in PD treatment. Baseline values were set to 100%. MTAC creatinine (closed circles), glucose absorption (open circles), transcapillary ultrafiltration (TCUFR) (closed squares), and the restriction coefficient (closed triangles) are given. No significant differences were found.
Chapter 12

PhD Portfolio
List of publications
Acknowledgements/Dankwoord
Curriculum vitae
Chapter 12

PhD Portfolio

Name: Anouk T.N. van Diepen
PhD Period: April 2011-Februari 2015
Promotores: Prof. dr. R.T. Krediet and Prof. dr. F.W. Dekker
Co-promotores: Dr. D.G. Struijk and Dr. T. Hoekstra

General courses

<table>
<thead>
<tr>
<th>Course</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDT course for Reviewers-to-be</td>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>Peritoneal Dialysis University</td>
<td>2013</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Specific Epidemiology courses

<table>
<thead>
<tr>
<th>Course</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced epidemiologic methods: part I</td>
<td>2014</td>
<td>1.0</td>
</tr>
<tr>
<td>Capita selecta</td>
<td>2014</td>
<td>3.0</td>
</tr>
<tr>
<td>Basic methods and reasoning in biostatistics</td>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>Causal Inference</td>
<td>2014</td>
<td>3.0</td>
</tr>
<tr>
<td>Design and organisation of clinical trials</td>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>Clinical epidemiology: study design and analysis</td>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>Study design and interpretation</td>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>Clinical epidemiology</td>
<td>2013</td>
<td>2.0</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>2013</td>
<td>2.0</td>
</tr>
<tr>
<td>Repeated measurements</td>
<td>2013</td>
<td>2.0</td>
</tr>
<tr>
<td>Survival analysis</td>
<td>2013</td>
<td>2.0</td>
</tr>
<tr>
<td>Roaming through methodology</td>
<td>2013</td>
<td>2.0</td>
</tr>
<tr>
<td>Regression analysis</td>
<td>2012</td>
<td>2.0</td>
</tr>
<tr>
<td>Basis principles of aetiologic research</td>
<td>2012</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Lectures, Symposia and Master Classes

<table>
<thead>
<tr>
<th>Course</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEON pre-conference course on instrumental variables</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>“New Kids on the block”; wetenschappelijk onderzoek in de Nefrologie</td>
<td>2014</td>
<td>0.2</td>
</tr>
<tr>
<td>Prof. dr. Miguel Hernan: “Evolution of Causal Inference”</td>
<td>2013</td>
<td>0.1</td>
</tr>
<tr>
<td>Masterclass clinical research and epidemiology</td>
<td>2012</td>
<td>2.0</td>
</tr>
</tbody>
</table>
### Oral presentations

<table>
<thead>
<tr>
<th>The association between glucose exposure and the risk of peritonitis in peritoneal dialysis patients</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 35th Annual dialysis conference</td>
<td>2015</td>
<td>0.5</td>
</tr>
<tr>
<td>The effect of high and low glucose on the time course of peritoneal transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peritoneal transport meeting</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>Protein-energy wasting is a risk factor for infections in both hemodialysis and peritoneal dialysis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PLAN day</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>• Nederlandse Nefrologiedagen</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>The first dialysis modality and the risk for dialysis technique and non-dialysis technique-related infectious complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 34th Annual Dialysis Conference</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>• NFN Najaarsymposium</td>
<td>2013</td>
<td>0.5</td>
</tr>
<tr>
<td>The mutual relationship between peritonitis and peritoneal transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 34th Annual Dialysis Conference</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>The first peritonitis episode alters the natural course of peritoneal membrane characteristics in peritoneal dialysis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 34th Annual Dialysis Conference</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>Effects of the first peritonitis and multiple peritonitis episodes on peritoneal transport</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peritoneal Transport Meeting</td>
<td>2013</td>
<td>0.5</td>
</tr>
<tr>
<td>First peritonitis episode influences peritoneal size-selectivity to macromolecules in peritoneal dialysis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 50th ERA-EDTA Congress</td>
<td>2013</td>
<td>0.5</td>
</tr>
<tr>
<td>The association between exit site infection and peritonitis in patients with end-stage renal disease treated with peritoneal dialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• 32nd Annual Dialysis Conference</td>
<td>2012</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Poster presentations

<table>
<thead>
<tr>
<th>The first dialysis modality and the risk for dialysis technique and non-dialysis technique-related infectious complications</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 51st ERA-EDTA congress</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>Protein-wasting is a risk factor for infectious complications in both hemodialysis and peritoneal dialysis patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ASN Kidney week</td>
<td>2014</td>
<td>0.5</td>
</tr>
<tr>
<td>• 17th International Congress of the ISRNM</td>
<td>2014</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Chapter 12

- 51st ERA-EDTA congress 2014 0.5
- 38th WEON conference 2014 0.5

The mutual relationship between peritonitis and peritoneal transport
- 11th European Peritoneal Dialysis Meeting 2013 0.5
- ASN Kidney Week 2013 0.5

The first peritonitis episode interferes with the natural course of peritoneal transport
- 11th European Peritoneal Dialysis Meeting 2013 0.5

 Trọng lượng các bài học

<table>
<thead>
<tr>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>0.2</td>
</tr>
<tr>
<td>2014</td>
<td>2.0</td>
</tr>
<tr>
<td>2014</td>
<td>0.4</td>
</tr>
<tr>
<td>2013</td>
<td>8.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(Inter)national Conferences</th>
<th>Year</th>
<th>ECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>15th Congress of the ISPD – Madrid, Spain</td>
<td>2014</td>
<td>1.0</td>
</tr>
<tr>
<td>38th WEON congress – Leiden, The Netherlands</td>
<td>2014</td>
<td>0.6</td>
</tr>
<tr>
<td>51st ERA-EDTA congress – Amsterdam, The Netherlands</td>
<td>2014</td>
<td>1.0</td>
</tr>
<tr>
<td>Peritoneal Transport Meeting – Amsterdam, The Netherlands</td>
<td>2014</td>
<td>0.2</td>
</tr>
<tr>
<td>17th International Congress of the ISRN – Würzburg, Germany</td>
<td>2014</td>
<td>1.0</td>
</tr>
<tr>
<td>Nederlandse Nefrologiedagen – Veldhoven, The Netherlands</td>
<td>2014</td>
<td>0.3</td>
</tr>
<tr>
<td>34th Annual Dialysis Conference – Atlanta, Georgia, USA</td>
<td>2014</td>
<td>1.0</td>
</tr>
<tr>
<td>Peritoneal Transport Meeting – Maastricht, The Netherlands</td>
<td>2013</td>
<td>0.2</td>
</tr>
<tr>
<td>NFN Najaarsymposium – Utrecht, The Netherlands</td>
<td>2013</td>
<td>0.2</td>
</tr>
<tr>
<td>Personalized Dialysis Initiatives – De Lutte, The Netherlands</td>
<td>2013</td>
<td>0.6</td>
</tr>
<tr>
<td>50th ERA-EDTA congress – Istanbul, Turkey</td>
<td>2013</td>
<td>1.0</td>
</tr>
<tr>
<td>32nd Annual Dialysis Conference – San Antonio, Texas, USA</td>
<td>2012</td>
<td>1.0</td>
</tr>
</tbody>
</table>
List of publications

THIS THESIS


OTHER PUBLICATIONS


*These authors contributed equally to the manuscript
Chapter 12

Acknowledgements/Dankwoord

Tot slot richt ik graag een woord van dank tot iedereen die direct of indirect heeft bijgedragen aan de totstandkoming van dit proefschrift.

Graag bedank ik alle patiënten die hebben deelgenomen aan de studies die gebruikt zijn voor dit proefschrift. De gepresenteerde resultaten zijn gebaseerd op de gegevens die hierdoor verzameld konden worden en zonder uw medewerking was dit niet mogelijk geweest. Bedankt!

Mijn promotor, prof. dr. R.T. Krediet, beste Ray, in mijn 4e geneeskunde studiejaar hielp u mij bij de organisatie van mijn wetenschappelijke stage in Toronto. Na deze stage heeft u zich ingezet zodat ik mijn onderzoek kon voortzetten in een promotietraject. Hartelijk dank dat u mij deze kans heeft gegeven! Uw aanstekelijke enthousiasme voor wetenschap en peritoneale dialyse, enorme kennis en ervaring en de manier waarop u altijd bereikbaar bent voor vragen maakte u een echte mentor tijdens mijn promotietraject. Ray, bedankt!

Mijn tweede promotor, prof. dr. F.W. Dekker, beste Friedo, ik wil jou bedanken voor het vertrouwen, de kansen en de ondersteuning die je mij hebt geboden. Hierdoor heb ik het opleidingstraject tot Epidemioloog B kunnen volgen en ervaring kunnen opdoen met de nationale coördinatie van een internationale studie (EQUAL). Het feit dat ik mijn (wetenschappelijk) ontwikkeling deels op jouw afdeling heb kunnen doormaken heeft mijn promotietraject absoluut verrijkt.

Mijn copromotor, dr. D.G. Struijk, beste Dick, ook jij hebt je ingezet zodat ik mijn onderzoek kon voortzetten in een promotietraject en hiervoor wil ik je hartelijk danken. Bovendien hebben jouw inspanningen om alle peritonitiden in het AMC in een database bij te houden dit proefschrift mede mogelijk gemaakt. Bedankt voor het meedenken over mijn vraagstellingen, de interpretatie van de analyses en de rappe feedback op mijn manuscripten.


Dear prof. dr. J.M. Bargman and the late prof. dr. D.G. Oreopoulos. I would like to thank you for giving me the opportunity to perform my scientific internship at the division of Nephrology in the Toronto General Hospital. My daily supervisor, dr. S.V. Jassal, dear Vanita, thank you for your guidance, interest and kindness. You are an incredible teacher and your passion for nephrology practice in the elderly has been enthusing. Without a doubt, your supervision during my first steps into the world of medical science has made a substantial contribution to this thesis.


Deirisa, met jou maakte ik mijn eerste congresreis. In het halen van vliegtuigen zijn we nooit heel goed geweest maar veel gelachen hebben we zeker! Bedankt, dat ik altijd bij jou kon binnenlopen met mijn (onderzoeksgereleaterde) vragen, voor de relativerende lunches en de gezelligheid. Ik ben dan ook heel blij dat jij als paranimf naast mij staat.

Dr. Marlies Noordzij, bedankt dat jij mij als geneeskundestudent wilde opnemen in de nefrologische literatuurbespreking van de afdeling Klinische Informatiekunde. Dit was een goede voorbereiding op mijn stage in Toronto.

De functieassistenten in het AMC wil ik graag bedanken voor de uitvoering van de vele SPAs en de bereidheid om vragen hierover te beantwoorden. In het bijzonder wil ik Marjan de Jong, PD verpleegkundige, bedanken voor haar uitleg over de CAPD/APD schema’s en bereikbaarheid voor vragen.

Mijn LUMC collega’s, staf, AIO’s en studenten: in het bijzonder de collega’s van het nierclubje. Graag wil ik jullie danken voor de leerzame bijeenkomsten en de open sfeer. Hakan, Jermaine, Christiaan en Merel, mijn EQUAL collega’s, bedankt voor de fantastische samenwerking waarin ik veel van jullie heb mogen leren. Hakan, succes met het afronden van jouw boekje en verdere carrière startend met de coschappen. Jermaine, veel succes met de Huisartsenopleiding. Chris, succes met jouw verdere opleiding tot Cardioloog. Merel, van...
jouw methodologische inbreng heb ik iedere week veel geleerd. Marit, ik ben heel blij dat ik de uren in de trein en in de medische archieven met jou heb mogen doorbrengen. Ons gezamenlijke doorzettingsvermogen, een goede dosis humor en veel koekjes hebben ons erdoorheen gesleept. Ook bedankt voor de goede samenwerking rondom de “Dwalingencursus”. Veel succes met de afronding van jouw boekje en de opleiding tot internist. Hugoline, kamergenote, dank voor de gezelligheid en jouw pogingen om mij meer te leren over de genetica. Veel succes met de afronding van jouw promotie en verdere carrière.

Dear international EQUAL colleagues, thank you for the educational experience and the wonderful collaboration. I am looking forward to the exciting results that EQUAL will produce in the near future.

Tamara Groen, Yvonne Souverein en Nancy de Boer, hartelijk dank voor de goede zorgen en de waardevolle secretariële ondersteuning.

Lieve vriendinnen, vrienden en familie, de ruimte hier is helaas te beperkt om jullie naam voor naam te noemen en aan te geven hoeveel jullie voor mij betekend hebben. Met name wil ik jullie bedanken voor de benodigde momenten van ontspanning: de sportieve activiteiten, etentjes, borrels, avondjes uit en weekendjes weg waren veelal onvergetelijk.

Lieve Wouter en José, jullie stonden en staan altijd voor mij klaar, zowel in zonnige als in moeilijkere tijden. Jullie rol in de totstandkoming van dit proefschrift is van niet te onderschatten waarde. Dank jullie wel!

Lieve Marinka, sinds een absurde tenniswedstrijd in ons zevende levensjaar zijn we vriendinnen. Ik vind het heel bijzonder dat jij na al die jaren naast mij staat als paranimf. Dank voor jouw interesse in mijn onderzoek en onvoorwaardelijke vriendschap.

Lieve Schoonfamilie, Mieke, Olav, Nils, Noor, Rie, Geert en wijlen Marjonel, de jaarlijkse wintersport en de maandelijkse dinertjes in Hilversum zijn altijd welkome momenten van ontspanning. Wat fijn dat ik daarvan mee mag genieten! Dank voor jullie openheid, warmte en betrokkenheid.

Kleine broertjes en zusjes worden groot: Lieve René, Pascal en Hedwig, ik ben enorm trots op jullie en de goede band die wij samen hebben. René, ik vind het heel knap dat jij zó zelfstandig woont en werkt. Pascal en Hedwig, dank voor jullie interesse in mijn onderzoek en dat jullie altijd voor mij klaarstaan. Eén voor allen, allen voor één!

Lieve mama en papa, mijn dank is groot en niet in woorden uit te drukken! Met name wil ik jullie bedanken voor het vertrouwen en de vrijheid die jullie mij hebben gegeven om mijn eigen keuzes te maken en de inspanningen die jullie hebben geleverd om mij daarbij te ondersteunen.

Tot slot, liefste Sven, dank voor jouw liefde, zorgzaamheid, humor, interesse, begrip, eerlijkheid, altijd nuchtere blik op de zaak en dat je er onvoorwaardelijk en altijd voor mij bent!
Curriculum vitae

Anouk Tessa Natasha van Diepen was born on February 19th 1990 in the VU medical center in Amsterdam as the daughter of Petrus Johannes Maria van Diepen en Joanna Francisca Maria van Diepen-Scholten. She grew up in Wervershoof, a small village in North Holland, with her brothers René and Pascal and her sister Hedwig. In 2007, she passed secondary school at the Tabor college, Oscar Romero (VWO, profile Nature and Health) in Hoorn after which she has started to study Medicine at the University of Amsterdam. In 2011, supported by a Kolff scholarship for students from the Dutch Kidney foundation, she performed her scientific internship at the Department of Nephrology of the Toronto General Hospital in Canada under supervision of dr. S.V. Jassal (Canada) and Prof. dr. R.T. Krediet (the Netherlands). In 2012 she earned her doctoral degree, after which she interrupted her medical study to continue her research as a full-time PhD student for the current thesis at the Department of Nephrology of the Academic Medical Center under supervision of Prof. dr. R.T. Krediet and Dr. D.G. Struijk. In the spring of 2013 she applied for, and obtained an ERA-EDTA short-term fellowship, which facilitated an exchange with the Department of Clinical Epidemiology of the Leiden University Medical Center (LUMC). The main purpose of the fellowship was to obtain epidemiological knowledge and practical skills by participation in epidemiological courses at this department. This was the start of her training to become an epidemiologist. From this moment on, her PhD research was partially performed at the LUMC under supervision of Prof. dr. F.W. Dekker and Dr. T. Hoekstra.

From October 2013, parallel to her PhD trajectory, she was one of the co-ordinators of the Dutch part of a new European study on treatment in advanced chronic kidney disease: the EQUAL study. During her PhD, Anouk has won a young investigator award for best abstract, was a nominee for best poster presentation and earned travel awards.

As of December 2014 she resumed her medical internships with the prospect to finish medical school and become a medical doctor in the spring of 2017.
INFECTIONS IN PERITONEAL DIALYSIS PATIENTS
Incidence, determinants and the association with peritoneal transport

Amsterdam 2015
Anouk T.N. van Diepen