Université de Montréal

Association of Patient to Nurse Ratio and Hand Washing Stations and Infection-Related Hospitalizations in Hemodialysis Patients

Présenté par Elaine Mong-Slezak

Département des Sciences Biomédicales, Université de Montréal
Faculté de Médicine

Mémoire présenté
en vue d'obtention du grade de M. Sc.
En Sciences Biomédicales
Option : Recherche Clinique

Juin, 2018

Résumé

Littérature et objectifs : L'infection est la deuxième cause de décès dans la population d'hémodialyse après la maladie cardiovasculaire. Cependant, les taux d'infection varient avec la facilité. Les variables au niveau de la facilité responsable de cette variation ne sont pas connues.

Méthodes : Une étude rétrospective de cohorte a été faite avec une cohorte de 6,124 patients adultes en hémodialyse chronique et 21 facilités d'hémodialyse participantes. Nous avons utilisé les données liées de la RAMQ et Med-Echo. Les patients ont été suivis du premier janvier 2007 au 31 mars 2013. Les patients recevant une greffe de rein, les patients recevant la dialyse péritonéale et les patients recevant l'hémodialyse à la maison ont été exclus de l'étude. Les variables au niveau de la facilité ont été obtenues par les mesures directes ou en s'entretenant avec le personnel dans les facilités participantes**.** Les variables au niveau de la facilité mesurées dans cette étude incluent : ratio patient-infirmier, distance moyenne de la station de dialyse à la station de lavage des mains ou au distributeur de produits à base d'alcool (DPBA) le plus proche, le ratio de la station de lavage des mains et le ratio du distributeur de produits à base d'alcool. Les associations entre ces variables au niveau de la facilité et les hospitalisations liées à l'infection (HLI) ont été estimés avec des modèles Cox à effets mixtes et courbes de Kaplan-Meier.

Résultats : Un ratio patient-infirmier de ≥4 (HR = 0.72, 95% CI = 0.55-0.95) et un ratio du DPBA de ≥1.5 (HR = 0.76, 95% CI = 0.60-0.95) ont été associés à un risque diminué des HLI. Une distance moyenne de la station de dialyse à la station de lavage des mains le plus proche de <4.75m (HR = 1.30, 95% CI = 1.03-1.64) et un ratio de la station de lavage des mains de <3.15 (HR = 1.38, 95% CI = 1.08-1.76) ont été associés à une augmentation de risque des HLI. Il n'a pas eu une association entre la distance moyenne de la station de dialyse au DPBA le plus proche à les HLI. Cependant, ces associations peuvent disparaitre en fonction de l'analyse de sensibilité effectuée.

Conclusion : La relation entre les HLI et les variables au niveau de la facilité analysée dans cette étude n'est pas clair.

Mots-clés : hémodialyse, hémodialyse chronique, infection, hospitalisations liées à l'infection, station de lavage des mains, distributeur de produits à base d'alcool

Abstract

Background and Objectives: Infection is the second most common cause of death in the hemodialysis population after cardiovascular disease. However, infection rates tend to vary depending on the dialysis facility. The facility-level variables responsible for this variation are unknown.

Methods: A retrospective cohort study was conducted with a cohort of 6,124 adult chronic hemodialysis patients in 21 participating dialysis facilities using linked data from two administrative databases (RAMQ and Med-Echo). Patients were followed from January 1, 2007 to March 31, 2013. Kidney transplant recipients, peritoneal dialysis patients and home hemodialysis patients were excluded. Facility-level variables were obtained by direct measurement or by interviewing the staff at participating facilities. Facility-level variables measured in this study include: patient to nurse ratio, mean distance of dialysis station to hand-washing station or alcohol-based hand rub dispenser (ABHRD), hand-washing station ratio and ABHRD ratio. The association between these facility-level variables and infection-related hospitalizations (IRH) was estimated using mixed effects Cox models and Kaplan-Meier curves.

Results: A patient to nurse ratio of ≥4 (HR = 0.72, 95% CI = 0.55-0.95) and an ABHRD ratio of ≥1.5 (HR = 0.76, 95% CI = 0.60-0.95) were associated with a significantly reduced risk of IRH. A mean distance from the dialysis station to the nearest washing station of <4.75 m (HR = 1.30, 95% CI = 1.03-1.64) and a hand-washing station ratio of <3.15 (HR = 1.38, 95% CI = 1.08-1.76) were associated with a significantly increased risk of IRH. There was no association between mean distance of dialysis station to ABHRD and risk of IRH. However, these associations disappeared depending on the sensitivity analysis done.

Conclusion: The association between IRH and the facility-level variables analyzed in this study is unclear.

Keywords: hemodialysis, chronic hemodialysis, infection, IRH, hand-washing station, sink, alcohol-based hand rub dispenser, ABHRD

Table of Contents

List of Tables

List of Figures

List of Acronyms and Abbreviations

ABHRD: Alcohol-based hand rub dispenser

ARB: Access-related bacteremia

AVF: Arteriovenous Fistula

AVG: Arteriovenous graft

CKD: Chronic Kidney Disease

CKD-MBD: Chronic Kidney Disease-Mineral Bone Disease

CVC: Central venous catheter

ESRD: End Stage Renal Disease

IRH: Infection-related hospitalization

MRSA: Methicillin resistant *Staphylococcus aureus*

S. aureus: *Staphylococcus aureus*

This thesis is dedicated to my family, for their unconditional love and support

Acknowledgements

I would first like to thank my supervisor, Dr. Jean-Philippe Lafrance, for his excellent guidance and support, which were crucial to my success in writing this thesis. I appreciate his availability and the suggestions and corrections he made that have improved my thesis.

I would like to thank Emilie René for collecting the facility-related data in this study and Naoual Elftouh for her amazing work as a statistician. I greatly appreciate the advice and support they have given me.

I would like to thank the Université de Montréal library staff for providing courses that helped me learn how to better use PubMed, Endnote and Microsoft Word. Using these resources has saved me a lot of time, and I appreciate everything I learned during these classes.

Lastly, I would like to thank everyone in the ophthalmology department who welcomed me and made me feel at home in Hôpital Maisonneuve-Rosemont.

Introduction

The kidneys are a pair of bean-shaped organs whose primary function is to filter solutes, excess water and nitrogen wastes from the blood. They are also responsible for maintaining electrolyte balance and producing erythropoietin (which is responsible for red blood cell maturation in the bone marrow), renin (which regulates blood pressure via the renin-angiotensin system) and calcitriol (an activated form of vitamin D).

Chronic kidney disease (CKD) is characterized by a progressive and irreversible decline in kidney function. Over time, as the kidneys slowly fail, CKD results in increased concentrations of urea, creatinine and other metabolites in blood plasma as the kidneys are unable to filter them into urine. This results in uremia and many biochemical and hormonal abnormalities.[1] Over time, CKD may progress to ESRD (end stage renal disease), the last stage of kidney failure.

The kidney has many functions, and the loss of function manifests in many ways. Almost every organ system is affected by kidney failure, including the nervous system, endocrine system, hematologic system, cardiovascular system, gastrointestinal system, peripheral vascular system and the skeletal system. The loss of renin production and fluid retention results in increased blood pressure and hypertension. The loss of erythropoietin production reduces red blood cell production, which makes ESRD patients prone to anemia. The loss of calcitriol results in decreased calcium absorption. The loss of kidney function results in retention of phosphorus and potassium, as the kidneys normally excrete the excess.[1]

Complications are numerous. Chronic kidney disease-mineral bone disease (CKD-MBD). CKD-MBD is a systemic disorder of bone and mineral metabolism characterized by abnormalities in calcium, phosphorus and parathyroid hormone metabolism, disturbances in bone remodeling and mineralization and vascular calcification.[2-4] Cardiovascular disease is a major complication of CKD and ESRD, and many patients suffer from accelerated atherosclerosis.[5] Hypertension is both a cause and complication of ESRD, and is associated with an increased risk of coronary artery disease, stroke and congestive heart failure.[1] Another well-known complication is dyslipidemia (another well-known risk factor for cardiovascular disease in the general population).[6, 7]

Background

End Stage Renal Disease

Definition

ESRD is the last stage of kidney failure and is irreversible. It has multiple causes, the most common being diabetes. Other frequent causes include hypertension, glomerulonephritis and cystic kidney disease.[1] While some residual kidney function may remain, the kidneys are no longer able to function sufficiently to support life.

These patients must turn to renal replacement therapy to survive. Given the scarcity of kidney transplants, most will require dialysis (either hemodialysis or peritoneal dialysis). However, while dialysis allows ESRD patients to survive, it cannot replicate all of the functions of the kidney and is no cure for ESRD. They are still at high risk for cardiovascular diseases, infection and hospitalization,[8] and have a poor five-year survival rate of around 44.3%.[9]

Epidemiology

One study estimated the prevalence of CKD in Canada at 3 million during 2007-2009 (12.5%).[10] The Canadian Organ Replacement Register (CORR) estimates that more than 37,000 patients suffer from ESRD, and of these, nearly 22,000 are on dialysis and more than 15,000 are living with a functional kidney transplant. 5,597 patients initiated renal replacement therapy in 2016, with 75% receiving hemodialysis at the start of their treatment. Diabetes is still the most common cause of ESRD, identified in approximately 38% of new ESRD cases in 2016.[9]

Renal Replacement Therapies

Hemodialysis

Hemodialysis uses a semi-permeable membrane to remove solutes by diffusion and (to a lesser extent) by convection. While diffusion is driven by the transmembrane concentration gradient, convection is driven by the transmembrane hydrostatic pressure. The pore size is small to

allow undesirable solutes (such as urea) to pass across the membrane, while preventing desirable, larger molecules from being lost during hemodialysis. Separation of solutes by size is a major function of the kidney, and dialyzers are designed to mimic that function. However, while kidneys reabsorb precious small molecules in the renal tubules, the dialyzer has no mechanisms to do the same. Fortunately, most of these small solutes are abundant and are relatively inexpensive to add to the dialysate solution to prevent their loss due to diffusion. It is interesting to note that the native kidneys are capable of clearing small solutes at a far greater rate than what it is required to sustain life. It helps explain why modern intermittent hemodialysis, despite its limited ability to clear solutes in comparison to native kidneys, is able to prolong the lives of dialysis patients.[1]

Hemodialysis can be done at a hospital where most of the work is taken care of by medical staff or at home with or without a caregiver.[11] Either way, patients will require erythropoietin to prevent anemia and calcitriol or its analogs to prevent or ameliorate CKD-MBD.[1] Iron may also be given to treat anemia and reduce the dose of erythropoietin.[12] However, it is unclear if iron use is associated with an increased risk of infection, as iron is essential for bacterial growth.[13]

Dialysis patients are also restricted in terms of diet.[11] For example, hemodialysis patients must limit the fluids, phosphorous, potassium and sodium they consume.[1, 14, 15] An excess of phosphorous can lead to hyperphosphatemia, which is associated with complications such as secondary hyperparathyroidism, arterial calcification and renal osteodystrophy. Sodium intake is limited in an effort to control hypertension and to avoid excessive thirst and fluid consumption.[14] Fluid intake is limited in the cases where dialysis cannot remove all of the excess fluid accumulated between dialysis sessions.[1, 15] Potassium intake is limited to avoid hyperkalemia, which is associated with arrhythmias and a multitude of heart problems. In the kidney, hyperkalemia reduces NH_4^+ excretion, leading to metabolic acidosis.[1]

Vascular Access

Hemodialysis is the most common form of renal replacement therapy[8, 9] and is done using a dialyzer machine. Hemodialysis requires vascular access in the form of a catheter, an

arteriovenous fistula or an arteriovenous graft to work, as it requires blood flow from the patient to the dialyzer and back.

Arteriovenous Fistula

The preferred type of vascular access is the arteriovenous fistula (AVF),[16-18] which is created by connecting a vein to an artery. Both vessels must be in close proximity and must be of sufficient size for the procedure to be successful.[1] The procedure allows some arterial blood to flow into the vein, strengthening it over time and allowing it to grow larger and thicker. This 'maturation' process takes one to three months to occur before the fistula can be used for hemodialysis. Once the fistula is mature, it will provide easy access for hemodialysis as the vein will be strong enough to be punctured repeatedly.[19] AVFs are the preferred vascular access type as they tend to last the longest, are less prone to infections and suffer less complications.[17, 18, 20]

Arteriovenous Graft

The second preferred type of vascular access is the arteriovenous graft (AVG).[21] It is often performed on patients whose blood vessels are unsuitable for the creation of AVFs. While an AVF is created using native blood vessels which are close to each other, an AVG is created using a prosthetic graft by connecting two blood vessels which are farther apart.[1, 17] AVGs usually require about 2-3 weeks to mature after the surgery is complete. If well-maintained, the graft can last for several years.[22] While AVGs tend to fail sooner than AVFs, are more prone to infection and suffer more complications (such as stenosis and thrombosis),[17] they are still associated with lower mortality rates than the last form of venous access: central venous catheters.[23-25]

Central Venous Catheters

Central venous catheters (CVCs) are plastic tubes inserted into a large vein, preferably the internal jugular vein, the femoral vein or the subclavian vein. CVCs do not require time to mature and can be inserted immediately.[17] However, it is well documented that they are even more prone to infection[23-27] and are associated with a greater risk of infection-related and all-cause mortality compared to AVFs and AVGs.[23, 24, 26, 28, 29] CVCs are also at high risk for

complications (such as thrombosis) and are less efficient than AVFs and AVGs at clearing solutes from the blood. Non-tunnelled and non-cuffed CVCs are often used in acute renal failure patients and (temporarily) in patients whose AVFs and AVGs fail. Tunnelled and cuffed CVCs are used by patients undergoing chronic dialysis.[17]

Prevalence of Vascular Access

In 2014, 80.3% of incident ESRD patients in the United States initiated hemodialysis with a CVC. However, fistula use increases over time, to the point where 44.3% of hemodialysis patients use an AVF after 12 months and only 13.6% sill dialyze using only a catheter.[30] In Quebec, tunneled catheters are still the most commonly used form of venous access for hemodialysis (58.3%), followed by AVFs (37.1%) and AVGs (3.6%).[31]

Peritoneal Dialysis

The second treatment for ESRD is peritoneal dialysis. The peritoneum is a thin, semi-permeable membrane that covers most of the abdominal wall and intra-abdominal organs. While hemodialysis relies on the dialyzer to provide a semi-permeable membrane to remove solutes from the blood, peritoneal dialysis uses the peritoneum as the dialysis membrane. Much like hemodialysis, solute transport occurs through both diffusion and convection.[1]

Peritoneal dialysis is done by transferring the dialysate fluid into the peritoneal cavity, waiting for a period of time for solutes to filter into the dialysis fluid (the 'dwell' period), then draining the waste-filled dialysate fluid and replacing it with fresh dialysate fluid. The dwell times can vary depending on the patient and the type of peritoneal dialysis received. Peritoneal dialysis can be done multiple times during the day or overnight. It can be done at work or at home, allowing patients more freedom.[11]

Peritoneal dialysis requires a catheter in order to transfer the dialysate fluid in and out of the peritoneal cavity. Possible complications include peritonitis (inflammation of the peritoneum) and catheter-related infection.[1] Much like hemodialysis patients, peritoneal dialysis patients are also limited in terms of diet (in terms of calories, salt and phosphorus).[11] Both hemodialysis and peritoneal dialysis are also prone to malnutrition and 'protein energy wasting,' a state where patients have reduced body protein and energy fuel. Malnutrition and

protein energy wasting are associated with increased morbidity and mortality as well as impaired quality of life.[14]

Kidney Transplantation

The most optimal form of kidney replacement therapy is kidney transplantation. Unfortunately, demand far outstrips supply, and patients may spend a considerable amount of time on the waiting list before a kidney becomes available. Once the transplant surgery is complete, the kidney transplant recipient must take immunosuppressants for as long as the graft functions to prevent their immune system from rejecting it.[11] However, kidney transplant recipients no longer require dialysis. They have more freedom to go about their daily lives, less dietary restrictions and a better survival rate. However, due to immunosuppression, infection remains a common complication of kidney transplantation.[1]

Implications for this Study

While there are multiple treatments available for ESRD, this research project only involves hemodialysis patients. Peritoneal dialysis patients are not included as peritoneal dialysis is done at home or work. They do not need to return to the dialysis unit regularly like hemodialysis patients. Home hemodialysis patients and kidney transplant recipients are also not included for similar reasons as peritoneal dialysis patients.

Infections in Hemodialysis Patients

Normal Function of the Immune System

The normal response to infection (and vaccines) involves activating both innate and adaptive immunity, allowing the immune system to recognize that particular antigen and mount a stronger and more effective response when it encounters it again. This requires the innate immune system to recognize the pathogen's antigens as foreign, the activation of dendritic cells and their migration to lymph nodes where they can present the antigen to naive T cells and B cells.

While T cells recognize the antigen in a processed form on the MHC class I or class II molecules, B cells can recognize the antigens in their native form. B cells that recognize the antigen they have an affinity with can then be activated by both T cells and dendritic cells, activating the humoral immune response.[32] B cells are responsible for producing antibodies as part of the humoral immune response. Upon exposure to an antigen, they either differentiate into plasma cells (which secrete antibodies) and memory B cells (which persist indefinitely and recognize that particular antigen).[33]

Naive T cells will differentiate into effector and memory T cells after successful activation by an antigen presenting cell, activating the cell-mediated immune response. Effector T cells either regulate the immune response via secretion of cytokines (as CD4+ helper cells) or destroy target cells (as CD8+ cytotoxic cells). After the infection has passed, a small minority will remain as memory T cells, allowing a far stronger and faster response if the same antigen is encountered again.

Immune Dysfunction in ESRD

In addition to all of the metabolic abnormalities and complications mentioned above, both CKD and ESRD patients suffer from uremia, a condition defined as the presence of organic waste solutes in the blood that are normally removed by the kidney.[34] These solutes include urea, some peptides and proteins, guanidines, phenols, indoles and aliphatic amines.[1] While little is known about which ones are toxic, uremia has an undeniable effect on the health of the

patient.[34] Uremic toxins are also associated with significant morbidity and mortality and play a role in the progression of cardiovascular disease in CKD and ESRD patients.[35] Manifestations of uremia include encephalopathy, cognitive impairment, peripheral neuropathy,[36, 37] loss of appetite,[38] sleep disturbances,[36] cardiomyopathy[39] and an impaired immune response.[33, 40-42]

Uremia in ESRD patients is associated with both immune activation as well as immune deficiency.[42] Systemic and chronic inflammation contributes to cardiovascular disease, atherosclerosis, cachexia and anemia suffered by ESRD patients.[43] The uremic environment in ESRD patients is one of systemic inflammation and oxidative stress.[33] Monocytes, macrophages and granulocytes are activated in the innate immune response, resulting in the production of cytokines and reactive oxygen species.[44, 45] Regulatory T cells, which are normally responsible for suppressing inflammation, have impaired inhibitory activity.[46] Despite the activation of monocytes and polymorphonuclear leukocytes, their ability to phagocytose pathogens is impaired in uremic conditions.[47, 48] It has been said that uremia causes premature aging of the immune system, as the immune systems of younger dialysis patients are similar to those of healthy, elderly individuals.[49, 50]

ESRD results in dendritic cell depletion and dysfunction.[51-53] As dendritic cells are one of the most important antigen-presenting cells and responsible for regulating adaptive and innate immunity, this diminishes their ability to present antigens to T cells and B cells and thus activate adaptive immunity.[33] Monocytes also have reduced expression of co-stimulatory molecules required for T cell activation, resulting in defects in antigen presentation.[42] Naive T cells and central memory cells are also depleted in uremic conditions, reducing the effectiveness of cell mediated immunity.[54-57] B cell numbers are also depleted due to apoptosis[58] and impaired maturation,[59] reducing the effectiveness of humoral immunity. All of these impairments contribute to the immunodeficiency experienced by ESRD patients, resulting in a reduced response to vaccines, higher incidence and severity of infections and poorer outcomes when compared to the general population.[33]

Epidemiology

Dialysis patients have a poor five-year survival rate of around 44.3%,[9] which is significantly worse than that of patients hospitalized with myocardial infarction (more than 70%)[60] or

diagnosed with colorectal cancer (64%).[61] Age and primary diagnosis have a considerable effect on survival. Younger patients have a higher five-year survival rate than elderly ones. The poorest survival rates are seen in patients with a primary diagnosis of renal vascular disease (38%), drug-induced renal failure (41%) and diabetes (48%). Patients with polycystic kidney disease and glomerulonephritis have the highest survival rates, at 76% and 66% respectively.[62]

In the United States, hemodialysis patients have an infection-related hospitalization (IRH) rate of 0.47 per patient-year. Older patients and those with diabetes as the primary cause of renal failure tend to have the highest rates of hospitalization. Peritoneal dialysis patients have the highest rate of admission for any infection at 573 per 1,000 patient years, while hemodialysis patients have the highest rate of admission for bacteremia/sepsis, at 108 per 1,000 patient years in 2009.[63]

In 2016-2017, the rate of bacteremia was 0.22 per 100 patient years in Quebec. The incidence of vascular access-related bloodstream infections was 32.7 times higher in patients using non-tunnelled catheters and 8.3 times higher in patients using tunneled catheters compared to the patients using a fistula without the buttonhole technique.[31] Another major risk factor for bacteremia is a history of previous bacteremia.[64-66]

Given that the skin microbiome consists mostly of gram-positive bacteria,[67] it is not surprising that most access-related infections are caused by gram-positive cocci. *Staphylococcus aureus* is the most common bacterial species[31, 64, 68-72] isolated in access-related infections, although the exact proportions vary depending on the location. For example, in Quebec, *Staphylococcus aureus* is found in 65% of isolates, followed by coagulase negative staphylococci (12%) and enterobacteria (12%).[31] *S. aureus* is the pathogen associated with the worst outcomes, the highest costs and the highest risk of complications.[72-75] In Quebec, *S. aureus* is the most common microorganism isolated in vascular access-related bloodstream infections resulting in death (44% of cases).[31] The morbidity and mortality associated with access-related infections is even higher if multi-resistant microorganisms are isolated, such as MRSA (methicillin resistant *Staphylococcus aureus*).[76]

Prevention

There are various ways to prevent or treat infections affecting dialysis patients. Prevention is key, given the costs and risks of complications associated with infection in this vulnerable population. Dialysis patients have impaired immune systems, and their immunodeficiency is worsened by factors such as low dialyzer biocompatibility, diabetes and administration of immunosuppressive medication. Dialysis catheters also disrupt the normal skin barrier, allowing bacteria easier access to the bloodstream.[77]

Increasing the Use of Arteriovenous Fistulas

Patients using CVCs are at the greatest risk of ARBs (access-related bacteremia), while AVF users have the lowest risk of infection.[27] Thus, one way to prevent ARBs is to minimize the number of patients using CVCs, and various programs (such HP2020 and the Fistula First Initiative) continue to work to promote the use of AVFs.[18, 30]

Hand Hygiene

Adhering to a rigorous hygiene procedure is also important in preventing the spread of infection, either by using alcohol-based rubs or soap and water. Hand hygiene should be performed before and after manipulating the catheter. Sterile gloves should be worn for inserting new catheters.[78] Multiple studies have shown that increasing hand hygiene compliance among health care workers is associated with reduced transmission of MRSA and nosocomial infections.[79-82]

Vaccines

Due to the immunodeficiency associated with uremia, ESRD patients do not respond as well to vaccines as healthy people. This results in a lower seroconversion rate, lower peak antibody titers and faster decline in protective antibody levels.[83, 84] As such, they may require higher or more frequent vaccine doses to reinforce their immunity.[85] Vaccinating patients in the earlier stages of CKD before they become dependant on dialysis results in a better immune response.[84] The hepatitis B vaccines, pneumococcal polysaccharide vaccine, the annual influenza vaccine, the tetanus-diphtheria toxoids and the varicella vaccine are all

recommended to adult dialysis patients.[85, 86] Live vaccines are avoided in dialysis patients (and other immunocompromised) patients due to the risk of vaccine-induced infections.[87]

However, there is currently no recommendation to vaccinate hemodialysis patients against *Staphylococcus aureus*, one of the major causes of nosocomial infections. Despite the morbidity and mortality associated with *S. aureus*, there is currently no vaccine available for clinical use.[85] One study found a significantly reduced response to the *S. aureus* Type 5 CP-EPA conjugate vaccine in ESRD patients compared with healthy controls. Protective antibody levels were only maintained for six months in ESRD patients.[88] Another study also demonstrated that while the StaphVAX vaccine was well tolerated, it only provided partial protection in ESRD patients that lasted for ~40 weeks.[89] Another study tested a higher dose of the same vaccine (StaphVAX, by Nabi Biopharmaceutical). It was well tolerated and provided partial protection against *S. aureus* bacteremia for 40 weeks. After 50 weeks, the reduction of S. aureus bacteremia of the vaccinated group compared to the placebo was no longer statistically significant.[90] Unfortunately, StaphVAX failed in a phase III clinical trial, and development was discontinued.[77, 91]

Eradicating *S. aureus* nasal carriage

It is known that *S. aureus* is part of the normal flora of the skin and nose, and most often colonizes the nose.[67] *S. aureus* nasal carriage in the nose is a major risk factor for S. aureus infection as the bacteria living in the nose acts as a reservoir.[72, 92-94] Thus, the bacteria are passed from the nose to the hands, and then from the hands to the skin, where they may infect the patient's graft or catheter.[72, 95] Entry to blood (in hemodialysis patients) or peritoneum (in peritoneal dialysis patients) may be due to contamination when handling the catheter or by the bacteria entering the catheter tunnel from the exit site.[72]

It has been shown that people who carry *S. aureus* in their nose often carry it on their hands as well,[95, 96] and *S. aureus* infections among nasal carriers are often caused by the same strain of bacteria that inhabits their nose.[92] Dialysis patients are known to carry *S. aureus* more frequently than in the general population, with rates varying between 45% and 62% in different centres.[97-99] *S. aureus* nasal carriage in the general population varies depending on

the country, being estimated at 18%[100]-24%[101] in the Netherlands, 37.1% in Mexico[102] and 28.6% in the United States.[103]

Mupirocin has been shown to be effective at reducing or eliminating *S. aureus* nasal and hand carriage, thus reducing the incidence of catheter-related in infections.[104-108] However, it must be administered long-term. Once treatment is stopped, *S. aureus* will recolonize a high proportion both patients and staff after several months.[92, 108]

Topical Antimicrobials

In addition to its use in eliminating *S. aureus* nasal and hand carriage, topical mupirocin has also been shown to be effective at reducing catheter-related bacteremias and prolonging catheter survival.[109] While resistance to mupirocin was not initially observed during the time of these studies,[107, 109] there have recently been reports of the emergence of new staphylococci strains that are resistant to mupirocin.[110-114] Other topical agents that have been shown to be effective in preventing infections include polysporin ointment[115] and Medihoney.[116]

Oral antibiotics

Oral rifampin is also effective prophylaxis against *S. aureus* infection,[93, 117] but is associated with unacceptable side effects in 12% of patients, mostly due to severe nausea and vomiting after the first course of therapy.[117] Rifampin also has other disadvantages such as gastrointestinal intolerance, drug interactions and allergic reactions.[72] Transient resistance has also been found in patients treated with rifampin.[93]

Antibiotic Lock

The antibiotic lock protocol is done by filling the catheter lumen with very high concentrations of antibiotics and leaving it there for hours or days.[118] This is based on the fact that most infections in long-term catheters originate in the catheter hub before spreading to the catheter lumen.[119] Antibiotic locks have been shown to be an effective prophylaxis against catheter-related infections.[120] Several studies have compared an antibiotic lock solution with the standard heparin-lock solution. All have reported a reduced incidence of catheter related infections in the antibiotic lock group compared with the heparin group.[121-129] Antibiotic or antimicrobial solutions used in these studies include citrate-taurolidine,[121, 129] gentamicin-

citrate,[122, 127, 128] cefazolin-gentamicin-heparin,[126] minocycline-EDTA,[127] cefotaxime-heparin,[124] 30% trisodium citrate[125] and gentamicin-heparin.[123]

Treatment

Empiric Antibiotic Therapy

In the case where a catheter-related bacteremia is suspected, empiric antibiotic therapy should be initiated immediately regardless of whether the pathogen has been identified from blood cultures. Given that either gram-positive or gram negative bacteria can cause bacteremia, empiric therapy must be effective against both.[130] Thus, the empiric initial regiment for treating catheter-related bacteremias should include vancomycin (effective against gram positive bacteria) and an aminoglycoside such as gentamycin or a third generation cephalosporin (effective against gram negative bacteria).[131-133] Once the pathogen and the antibiotics it is sensitive to are identified, it is important to switch to the most narrow spectrum antibiotic that is feasible. This is done to limit the development of antibiotic resistance.[133]

Biofilms

If catheters are colonized by pathogenic bacteria, those bacteria will form a biofilm on the outer surface of the catheter or the catheter lumen.[134, 135] Biofilm formation is a step-wise process that starts when free-floating planktonic cells attach to the surface and form microcolonies.[134] Up until this point, the biofilm formation is considered reversible. However, once bacterial communication begins (called 'quorum-sensing'), the bacteria will begin to organize themselves into a biofilm. They eventually start the production and secretion of exopolysaccharides, after which biofilm formation becomes irreversible.[134, 136] Over time, the biofilm matures, growing in size. Once mature, and if they sense adverse conditions, the bacteria will disperse in planktonic form and colonize a new site.[134] In the case of patients with CVCs, this dispersion results in bacteremia as the catheter allows the bacteria easy access to the bloodstream.[135, 137, 138]

Treatment of biofilms is difficult as bacteria within a biofilm can tolerate high concentrations of antibiotics and are adept at evading host defenses, including phagocytosis.[137, 139, 140] This is different from antibiotic resistance, as the bacteria may be susceptible to antibiotics in

planktonic form, but they are protected when residing within a biofilm.[137, 139-141] If the biofilm is disrupted, the bacteria within will once again become sensitive to antibiotics.[137] Antibiotics may have delayed and/or reduced penetration in biofilms, and the biofilm's microenvironment may inhibit antibiotic activity, as some antibiotics are less effective in anaerobic or low pH environments.[139]

Persister cells are a tiny minority of cells that often survive antibiotic therapy. Once antibiotic treatment is stopped, they will become active, repopulate the biofilm and eventually cause another infection.[139] They are believed to be the result of a phenotypic switch, as many of the bacteria regrown from them remain sensitive to the antibiotic.[142] While it has been shown that E. coli persisters are non-growing prior to antibiotic exposure,[142] they may not necessarily be dormant. Persisters have very different gene expression profiles compared to both growing and non-growing cells. It has been proposed that instead of preventing an antibiotic from binding to its target (as is the case with antibiotic resistant cells), persisters block the essential targets of antibiotics, resulting in a partially dormant, multidrug tolerant cell.[143]

Treatment and Prevention of Biofilms

The most efficient way to treat chronic infections caused by biofilms is to remove the catheter,[137-140] especially in the case of a tunnel infection.[144] However, successful treatment without removing the catheter ('catheter salvage') is possible in some cases. However, success rates tend to vary.[64, 145] If the infection is restricted to the exit site, catheter removal may not be necessary; they can be salvaged with topical and oral antibiotics.[146, 147]

Various means of treating or preventing the development of biofilms have been proposed, including using materials that inhibit bacterial adhesion,[148-151] inhibition of bacterial adhesions[152] and their receptors,[153] using lactoferrin (an iron chelator) to inhibit adhesion,[154] vaccination against bacterial biofilm antigens[155] and use of non-pathogenic bacteria to prevent colonization.[156-158] Other proposed treatments against already formed biofilms include phage therapy,[159, 160] inducing dispersal of the biofilm[161] and use of adjuvants to increase antibiotic activity against persisters.[162-164] Potential adjuvants have been found in marine sponges, which use many anti-biofilm compounds to protect themselves and communicate with symbiotic organisms.[136]

Antibiotic Lock and Systemic Antibiotics

CRBs are usually treated with systemic antibiotics and removal of the infected catheter, but some studies have shown that using an antibiotic lock to eliminate biofilm in combination with systemic antibiotics can result in catheter salvage about 65-70% of the time.[165-167] Those same studies also show that the antibiotic lock protocol's success depends on the pathogen involved, with gram negative bacteria having the highest cure rate and *S. aureus* having the lowest cure rate.[130]

Antibiotic Resistance

While the effectiveness of antibiotics in the treatment or prevention of infections in dialysis patients is supported by the literature, there are concerns of antibiotic resistance with long-term use.[93, 108, 113, 114, 168, 169] These concerns are not unjustified; *S. aureus* and other bacteria have a long history of developing resistance to the antibiotics used against them.

Before 1946, 85% of *S. aureus* strains were susceptible to penicillin. Resistance became evident only a few years after penicillin's introduction, and now only 11% of strains are still susceptible to penicillin.[170] Methicillin was a penicillin derivative developed to circumvent penicillin resistance, but before long, reports emerged of methicillin resistant strains.[171-177] Gentamicin resistance has also been documented among gram-positive bacteria,[176-179] while gram-negative bacteria have become resistant to aminoglycosides.[180-183]

Vancomycin

Vancomycin is the antibiotic of choice in treating MRSA[184, 185] and is frequently used in treating or preventing MRSA in dialysis patients.[185-188] Guidelines have been made that recommend restricting the use of vancomycin in an effort to prevent the emergence or spread of resistance.[118] However, the cycle has repeated itself once again, and there have been numerous reports of vancomycin resistance emerging in *S. aureus*,[184, 189-191] coagulase-negative staphylococci[184, 192, 193] and enterococci.[194-199] The increasing prevalence of vancomycin intermediate *S. aureus* (VISA) strains worldwide is worrying, as VISA arises from fully susceptible isolates and is associated with glycopeptide treatment failure.[200] Despite widespread use of vancomycin, fully resistant strains of MRSA are mercifully rare.[201] Their

limited spread is likely due to a restriction modification system limiting the uptake of foreign DNA [202] and the fitness cost associated with vancomycin resistance.[203]

Controlling the Spread of Antibiotic Resistance

It has been suggested that the emergence and spread of these antibiotic resistant pathogens is promoted by poor infection control techniques and selective pressure due to liberal use of antibiotics.[199] Various recommendations have been made to control the spread of vancomycin resistant enterococci, including limiting the use of vancomycin, routinely testing isolates for vancomycin resistance and initiating isolation precautions to prevent the spread of enterococci between patients. These isolation precautions include isolating patients with vancomycin resistant enterococci, wearing gloves and gowns before entering these isolation rooms, removing them before leaving the room and immediately washing hands with an antiseptic agent.[204] Educating healthcare workers and patients and their families, environmental decontamination and adherence to hand hygiene is also important for any infection control program.[205]

Knowledge Gaps

It is notable that ARB rates still vary by facility despite similar proportions of catheter use. This suggests that other factors may influence ARB rates.[27, 206-209] There are relatively few studies that aim to determine risk factors for IRH, and those that are available focus on patient level risk factors.[25, 209-212]

Facility level risk factors are at least as important as patient-level risk factors. Modifying facility level risk factors may prevent infections in hemodialysis patients and perhaps affect a larger subset of the population at once. Each facility varies in the care it provides to its patients, and those variations may lead to different outcomes in terms of morbidity and morbidity in the dialysis population. There are many ways in which these dialysis facilities differ but this study will focus on hand hygiene, one of the cornerstones of nosocomial infection prevention.

There is also a lack of studies studying the effects of hand hygiene and nurse staffing (in this case, patient to nurse ratio) in the hemodialysis patient population. Many studies related to

hand hygiene focus on their effects on infection rates[213-217] or improving compliance[79, 80, 216, 218-222] in the general hospital milieu, the surgical ward or the intensive care unit. Studies related to nurse staffing usually focus on the Intensive Care Unit (ICU).[223-225] the Neonatal Intensive Care Unit (NICU)[226] or the hospital in general.[227]

Preface of Articles 1 and 2

The purpose of this study is to elucidate the relationship between various facility-level variables and the incidence of IRH. It is a retrospective cohort study involving incident and prevalent chronic dialysis patient and linked data from two large government databases: RAMQ and Med-Echo. Facility-level variables were collected by direct measurement or by interviewing the staff.

The first article will focus on the association between patient to nurse ratio and IRH rates. The hypothesis is that a higher patient to nurse ratio results in a higher nurse workload, reducing hand hygiene adherence and resulting in a higher incidence of IRHs.

The second article will focus on the association between various facility-level variables and IRH rates. These facility level variables include the hand-washing station ratio, ABHRD (alcohol-based hand rub dispenser) ratio and mean distance of dialysis to nearest hand-washing station/ABHRD. The hypothesis is that if these hand-washing stations and ABHRDs are less numerous or less accessible, it would reduce hand hygiene adherence and result in a higher incidence of IRHs.

Article 1: Association between Patient to Nurse Ratio and Infection-Related Hospitalizations in Hemodialysis Patients

Elaine Mong-Slezak,[1] Émilie René,[1] Naoual Elftouh,[1] Jean-Philippe Lafrance[1, 2, 3]

1 Maisonneuve-Rosemont Hospital Research Center, Montreal, Canada

2 Department of Pharmacology and Physiology, University of Montreal, Montreal, Canada

3 Division of Nephrology, Maisonneuve-Rosemont Hospital, 5415, boul. de l'Assomption, Montreal, QC H1T 2M4 Canada

Introduction

The largest segment of the healthcare workforce in both the United States[228] and Canada[229] consists of nurses. They provide bedside care and are essential in preventing and controlling healthcare associated infections.[230] Unfortunately, the nursing profession faces many problems that impact the care nurses are able to provide. There is a nursing shortage in both the United States[231-233] and Canada,[229, 233] resulting from too few graduating nurses and many nurses leaving the profession due to stress, poor working conditions and poor morale.[229] Nurses also experience high levels of burnout and job dissatisfaction, likely contributing to their desire to leave their profession.[233]

A higher patient to nurse ratio (or lower nurse to patient ratio) is a measure of nurse workload and is a proxy for decreased compliance to aseptic protocol. A higher patient to nurse ratio has been associated with higher odds of burnout and job dissatisfaction,[231] as well as higher risk of infection and complications in intensive care.[224, 234-238] Higher nurse staffing and higher workloads are also associated with higher mortality in the intensive care unit, but not in the rest of the hospital. This is likely due to the effects of nurse surveillance.[225] Methicillin resistant Staphylococcus aureus (MRSA) infections have been temporally associated with periods of understaffing and less attention to aseptic protocol.[239] Multiple studies have also observed that infection rates decline as hand hygiene compliance increases.[79, 81, 82, 240, 241]

The purpose of this study is to find out if there is an association between a higher patient to nurse ratio and higher rates of infection-related hospitalisation (IRH) in chronic hemodialysis patients. While multiple similar studies have been done in intensive care wards and surgical wards, none have been done in the hemodialysis population.

Patients and Methods

Study Design

This was a retrospective cohort study of incident and prevalent chronic dialysis patients. Patient-related data was extracted from the RAMQ and Med-Echo databases described below. Database linkage was done by RAMQ. The data on the facilities' patient to nurse ratio was collected from the 21 participating dialysis facilities by interviewing the staff.

Databases

Régie de l'assurance maladie du Québec (RAMQ)

The RAMQ provides free healthcare insurance for all Quebec residents. It is notable for covering all dialysis treatments and transplant surgeries, except for military personnel and First Nations. The RAMQ database contains registration files of the people it insures, which includes demographic information, information on pharmaceutical services (drugs and cost of drugs dispensed to insured people) and information on medical services provided, diagnosis and reimbursements transmitted by professionals to the RAMQ.

Québec hospital discharge summary database (Med-Echo)

The Med-Echo database was created in April 1976 and is owned by the Department of Health and Social Services. It is currently housed at RAMQ's facilities and contains clinical and administrative data relating to physical and mental health. It includes primary and up to 15 secondary discharge diagnoses, procedures performed in-hospital, admission and discharge dates and in-hospital mortality. Since 2006, Med-Echo uses ICD-10 codes for diagnoses.

Study Population

Our cohort included all patients who initiated (incident) or were currently receiving hemodialysis treatments (prevalent) between January 1, 2007 and March 31, 2013 at 21 participating dialysis facilities. All patients must have been at least 18 years of age or older at cohort entry, and must have been on chronic hemodialysis (defined as still receiving dialysis

after 90 days). The date of cohort entry was January 1, 2007 for prevalent patients and at initiation of chronic hemodialysis for incident patients.

The construction of the cohort was done by identifying all dialysis diagnostics, billings and procedures between October 1, 2006 and March 31, 2013 and counting the number of dialysis services for each patient. The relevant codes may be found in Table 13 in Appendix I.

Patients who received a kidney transplant prior to dialysis initiation were excluded by identifying all diagnostics, billings and procedures relating to kidney transplants prior to the first dialysis code in the study period. Transplant recipients were excluded from this study as they experience different types and rates of infections and better survival rates compared to hemodialysis patients[63] and because they no longer need to return to the dialysis facility regularly for dialysis.

To select patients who were truly on chronic dialysis (and not on acute dialysis), we used an algorithm that selects all dialysis codes in a 90-day window for a given dialysis code. Three criteria were evaluated to ascertain whether a patient is on chronic hemodialysis and for how long:

1) At least 3 in-center hemodialysis codes between day 75 and 90
2) Or at least 2 satellite hemodialysis unit supervision codes
3) Or a 1 satellite hemodialysis unit supervision between day 60 and 90

This algorithm is applied chronologically on each dialysis code, the first of which is considered as the date of entry into the cohort for that particular patient. In Quebec, each in-center hemodialysis treatment is billed by the attending nephrologist (one code for each patient per treatment). For satellite units, each treatment cannot be billed, but the attending nephrologist bills once a month for the supervision of the unit (one code for each patient per month). All patients who were not receiving chronic hemodialysis were excluded. This includes patients whose follow-up ended before January 1 2007, patients with less than 3 months of follow-up after cohort entry and patients not satisfying the above algorithm.

If a patient has more than three hemodialysis codes between days 75 and 90, then they were considered to be on hemodialysis. If not, we considered their dialysis modality to be the same

as the last dialysis code in the 90 days after cohort entry. Patients undergoing peritoneal dialysis or home hemodialysis were excluded, as infection rates and types vary greatly by modality[242] and because home hemodialysis and peritoneal dialysis are done outside of the hospital or satellite unit where the patient to nurse ratio does not apply. If a patient chose to transfer to a different modality (to peritoneal dialysis or home hemodialysis), the last date of follow-up corresponded to the date of modality transfer. If there was a gap of at least 30 (hospital) or 60 days (satellite unit) between two hemodialysis services, follow-up was stopped.

Each patient undergoes hemodialysis at a certain dialysis facility. While most continued hemodialysis at the same facility, some may choose to switch to another. Patients were considered to have switched facilities if they have at least two successive dialysis services in another facility. Patients without any period of follow-up in a participating dialysis facility were excluded.

Study patients were followed from their date of cohort entry until the earliest date of date of death, transplant, discontinuation of hemodialysis, modality transfer to peritoneal dialysis or home hemodialysis or the end of the study.

Outcome

Infection-related hospitalization

An IRH is defined as a hospitalization in which an infection is the principal diagnosis. Type of hospitalization and infection on the discharge sheet is classified using ICD-10 codes (see Table 15 in Appendix I for specific codes). IRHs were further categorized into 8 mutually exclusive categories based on the type of infection. Types of infection included abdominal, access-related, genitourinary, musculoskeletal, pneumonia, septicemia, skin and other infections, as these are the most important types of infection in this population.

Assessment of Facility-Level Variables

The patient to nurse ratio for this study ratio was defined as the number of patients divided by the number of nurses attending patients. It was evaluated once every 3 months for a total of 3

measurements to account for seasonal changes. Thus, it is possible for a single facility to be associated with more than one value of patient to nurse ratio due to it changing over the course of the study. However, some facilities were lost to follow-up. In these cases, only the initial measurement of the patient to nurse ratio is known.

Patient-to-nurse ratio was categorized using approximation of the first, second and third quartiles: <3, ≥ 3 and <4 or ≥ 4. A patient could end up in a 'missing' category if they suffer an IRH in a facility where the patient to nurse ratio is unknown (i.e. in a center that is not participating in this study). These patients were still part of the cohort (as they have a period of follow-up in a participating facility), but their patient to nurse ratio at the time of the IRH is not known as it is tied to the facility where they received their last dialysis service. In our analysis, these patients were represented as the 'unknown' category.

Assessment of Covariates

Baseline patient characteristics assessed at the date of cohort entry included age, sex and incident dialysis status (*versus* prevalent). Comorbidities were assessed two years before the cohort entry date. Comorbidities were identified with ICD-9 codes and ICD-10 codes from RAMQ data (see Table 14 in Appendix I for specific codes).

Comorbidities assessed include hospitalization in the prior year, hemodialysis incidence, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, cirrhosis or chronic liver disease, congestive heart failure, diabetes, history of amputation, hyperlipidemia, hypertension, malignancy, peripheral vascular disease, valvular disease, prior IRH or steroid use. Steroid use was assessed six months prior to cohort entry. A patient is considered to be using steroids if they have at least one prescription in the six months prior to their entry into the cohort and were using RAMQ's drug plan insurance.

Statistical Analysis

For baseline characteristics, we used mean, standard deviation, median and interquartile range to describe continuous variables such as age and follow-up. We used frequencies to describe categorical variables such as comorbidities and drug use.

Incidence Rate

For this study, we calculated IRH incidence rates by dividing the total number of IRH by the total number of years of follow-up. In this study, it is presented as the incidence rate per patient-year. The Poisson distribution was used to calculate the 95% confidence intervals (CI).

Kaplan-Meier

We used the Kaplan-Meier analysis to determine infection-free survival curves and probability of survival, stratified by patient to nurse ratio. The difference between the four survival curves was assessed with the log rank test.

Mixed Effects Cox Model

Conventional regression models assume that each patient is independent of one another. However, this is may not necessarily be true in multicentre studies like this one. For example, patients within the same 'cluster' (in this case, dialysis facility) are likely to have outcomes that are correlated with one another since they receive similar care under similar conditions. This violates the assumption of independent events and precludes us from using a conventional regression model. Analysis of multilevel data requires the use of mixed effect (or *hierarchical*) models.

In addition to patients being exposed to similar conditions within the same dialysis facility, they may also be a heterogeneous population. Within a heterogeneous population, there is one or more subsets of the population that are more susceptible to the event of interest than others. These individuals tend to experience the event first, leaving behind the less susceptible individuals in the cohort. As a result, the population hazard may appear to decrease with time even if the individual hazards are constant. If left uncorrected, it will result in the regression coefficients being underestimated.

A mixed effects Cox model can adjust for heterogeneity, and is defined as a survival regression model that incorporates *mixed effects*. It includes both fixed effects coefficients (which are constant within a given cluster) and random effects coefficients (which vary between individuals).

There was one Cox model used in the main analysis: a mixed effects Cox model for the first IRH with the facility as a random effect. In this case, the facility related variable was the patient to nurse ratio. The model was adjusted for all covariates listed above.

Sensitivity analyses

Four different sensitivity analyses were done to test the robustness of our results. The first sensitivity analysis examined what would happen if the largest facility was excluded from the analysis, as it appeared to highly influence our results. The second analysis excluded prevalent patients and only kept incident patients in the analyses. The third analysis tested whether patients switching facilities had any effect on the results. Thus, any patient with follow-up in more than one facility was excluded from the analysis.

In the main analysis, steroid use was not included due to the numerous missing values (21.7%). This is because data for this variable comes from the RAMQ, which also covers drug prescriptions through their public prescription drug insurance plan. Patients who were not covered by the public prescription drug insurance plan or who rely on private insurance were not included in RAMQ data, so their drug prescriptions were unknown in this study. Thus, we decided to do a fourth sensitivity analysis to check whether steroid use affected our results.

The analysis was done using SAS statistical software. In all cases, a result was considered statistically significant at a p-value of < 0.05.

Results

Description of baseline characteristics

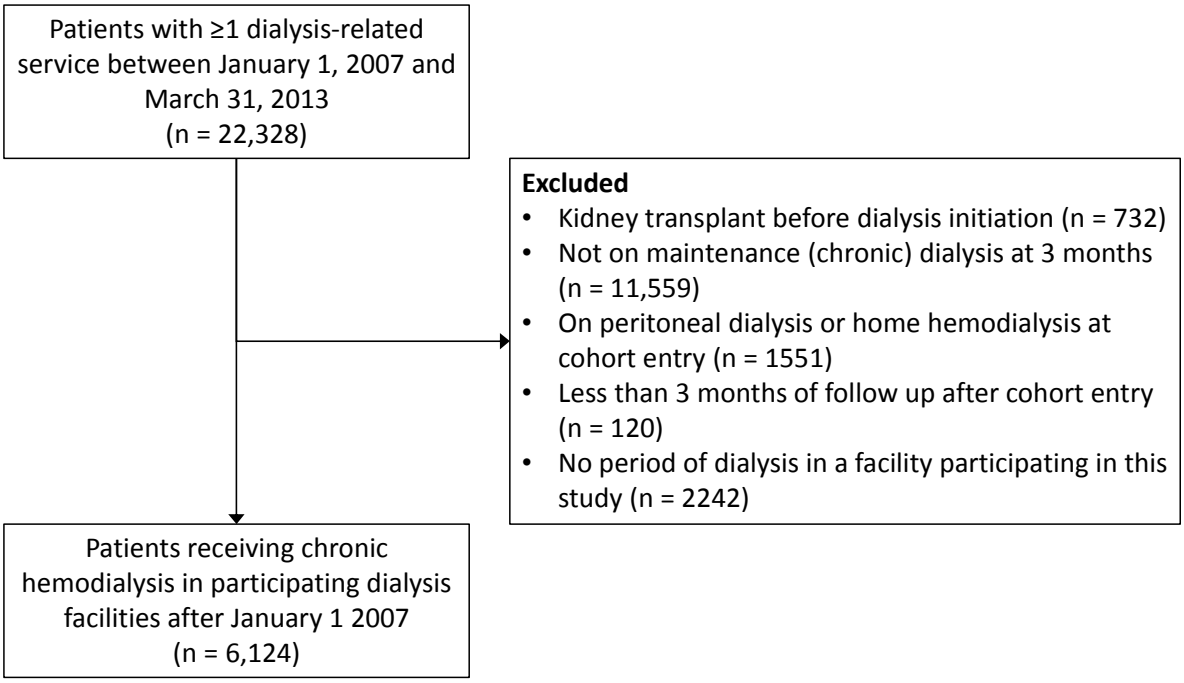

Figure 1. Summary of the construction of the cohort.

This study included 6,124 chronic hemodialysis patients in 21 participating dialysis facilities in the final cohort. An important number of patients were excluded due to not being on maintenance (chronic) dialysis. This is expected as dialysis can also be used for acute kidney failure, which can be followed by renal function recovery or death.

The distribution based on patient to nurse ratio can be seen in Table 1. 8 facilities had a mean patient to nurse ratio of <3. 8 facilities had a patient to nurse ratio of ≥3 and <4. 7 facilities had a patient to nurse ratio of ≥4. 417 (6.8%) patients had an unknown patient to nurse ratio (which is considered as a missing value).

Baseline characteristics are summarized in Table 1. The median age was 68.7 years, with an interquartile range of 58.2-77.0. The median follow-up was 2.0 years with an interquartile range of 0.9-3.8 years. The median and interquartile range were given in these two cases as neither age nor follow-up were normally distributed in this cohort. 39.9% of the patients were

female and 61.8% of them were incident patients. 50.7% of patients suffered from diabetes, 48.0% from cardiovascular disease and 70.8% from hypertension. 19.7% of patients had suffered an IRH prior to their entry into the cohort. There was no statistically significant difference in gender distribution among the four strata. Age distribution was also very similar among the patients whose patient to nurse ratio was known, although patients with a patient to nurse ratio of ≥3 and <4 tended to be slightly younger.

However, there were numerous differences in the presence of various comorbidities in the four strata except cerebrovascular disease, chronic pulmonary disease, diabetes and history of amputation. For example, cardiovascular disease was significantly more common in the group with a patient to nurse ratio of <3 ($p < 0.0001$), as were congestive heart failure ($p = 0.01$), valvular disease ($p = 0.006$) and incident hemodialysis patients ($p = 0.01$). Hypertension was significantly more common in the group with a patient to nurse ratio of ≥4 ($p < 0.0004$). Peripheral vascular disease was significantly more common among patients with a patient to nurse ratio of ≥4 or with an unknown patient to nurse ratio ($p < 0.0001$).

Covariates	Patient to nurse ratio					p-value
	All patients	<3	3 to <4	≥4	Unknown**	
	n=6124 (%)	n=2244 (%)	n=1692 (%)	n=1771 (%)	n=417 (%)	
Age (years)*	68.7 (58.2-77.0)	69.3 (58.7 -77.3)	68.6 (58.0-76.9)	69 (59.3 - 77.5)	69.9 (53.4 - 73.7)	<.0001
Sex (female)	2443 (39.9)	907 (40.4)	682 (40.31)	693 (39.1)	161 (38.6)	0.78
Hospitalization in prior year	3973 (64.9)	1514 (67.5)	1074 (63.5)	1119 (63.2)	266 (63.8)	0.06
Hemodialysis incidence	3786 (61.8)	1377 (61.4)	1026 (60.6)	1101 (62.2)	282 (67.6)	0.01
Cardiovascular disease	2940 (48.0)	1146 (51.1)	833 (49.2)	806 (45.5)	155 (37.2)	<.0001
Cerebrovascular disease	429 (7.0)	178 (7.9)	110 (6.5)	117 (6.6)	24 (5.8)	0.17
Chronic pulmonary disease	1147 (18.7)	437 (19.5)	304 (18.0)	335 (18.9)	71 (17.0)	0.51
Cirrhosis or chronic liver disease	281 (4.6)	99 (4.4)	73 (4.3)	95 (5.4)	14 (3.4)	0.23
Congestive heart failure	1662 (27.1)	657 (29.3)	442 (26.1)	469 (26.5)	94 (22.5)	0.01
Diabetes	3104 (50.7)	1127 (50.2)	883 (52.2)	900 (50.8)	194 (46.5)	0.20
History of amputation	144 (2.4)	59 (2.6)	37 (2.2)	38 (2.2)	10 (2.4)	0.73
Hyperlipidemia	3654 (59.7)	1385 (61.7)	999 (59.0)	1034 (58.4)	236 (56.6)	0.07
Hypertension	4338 (70.8)	1542 (68.7)	1229 (72.6)	1295 (73.1)	272 (65.2)	0.0004
Malignancy	1070 (17.5)	428 (19.1)	281 (16.6)	300 (16.9)	61 (14.6)	0.06
Peripheral vascular disease	1497 (24.4)	515 (23.0)	375 (22.2)	481 (27.2)	126 (30.2)	<.0001
Valvular disease	695 (11.3)	289 (12.9)	172 (10.2)	201 (11.4)	33 (7.9)	0.006
Prior IRH	1207 (19.7)	441 (19.7)	325 (19.2)	374 (21.1)	67 (16.1)	0.11

* Median (IQR)

** Unknown patient to nurse ratio

IRH, infection-related hospitalization; IQR, interquartile range

Table 1. Baseline characteristics stratified by patient to nurse ratio

Patient to Nurse Ratio Results

The results of the mixed effects Cox model used to analyze whether the mean patient to nurse ratio of a facility is associated with a greater risk of suffering their first IRH are shown in Table 2. A patient to nurse ratio of ≥3 and <4 was used as a reference. Given that the patient to nurse ratio was stratified based on quartiles, the middle quartile was the most conservative choice as a reference. While we would be less likely to see differences between the different strata with this reference point, any statistically significant differences that are found are more likely to be real.

A patient to nurse ratio of ≥4 was associated with a reduced risk of IRH in the adjusted model. No association was found between IRH and a patient to nurse ratio of <3. In the adjusted model, the following covariates were associated with a greater risk of IRH: hemodialysis incidence, hospitalization in the prior year, chronic pulmonary disease, history of amputation and prior IRH.

Covariates	**Mixed Effects Cox Model**	
	Unadjusted HR	**Adjusted HR**
	HR (95% CI)	
Mean Patient to Nurse Ratio		
Less than 3 (<3)	1.14 (0.82, 1.58)	1.12 (0.83, 1.51)
3 to less than 4 (3 to <4)	Reference	
4 or more (4≤)	0.66 (0.50, 1.47)	0.72 (0.55, 0.95)
Unknown	0.90 (0.55, 1.30)	0.97 (0.61, 1.53)
Age (years)*	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Sex (female)	0.96 (0.87, 1.05)	0.96 (0.87, 1.05)
Hemodialysis incidence	1.46 (1.32, 1.61)	1.13 (1.02, 1.24)
Hospitalization in prior year	1.10 (1.00, 1.21)	1.19 (1.06, 1.33)
Cardiovascular disease	1.27 (1.16, 1.39)	0.99 (0.89, 1.10)
Cerebrovascular disease	1.49 (1.28, 1.74)	1.18 (1.00, 1.39)
Chronic pulmonary disease	1.90 (1.71, 2.11)	1.57 (1.40, 1.76)
Cirrhosis or chronic liver disease	1.44 (1.18, 1.77)	1.18 (0.96, 1.44)
Congestive heart failure	1.41 (1.27, 1.55)	1.10 (0.98, 1.23)
Diabetes	1.29 (1.17, 1.41)	1.08 (0.98, 1.19)
History of amputation	1.80 (1.39, 2.32)	1.37 (1.05, 1.80)
Hyperlipidemia	1.15 (1.05, 1.27)	1.04 (0.93, 1.15)
Hypertension	1.26 (1.13, 1.40)	0.91 (0.80, 1.02)
Malignancy	1.24 (1.10, 1.39)	1.12 (0.99, 1.26)
Peripheral vascular disease	1.36 (1.23, 1.51)	1.05 (0.93, 1.18)
Valvular disease	1.24 (1.08, 1.43)	1.00 (0.86, 1.15)
Prior IRH	1.97 (1.78, 2.19)	1.67 (1.49, 1.86)

HR, hazard ratio; CI, confidence interval; IRH, infection-related hospitalization

Table 2. Mixed effects Cox model for first IRH (patient to nurse ratio)

Kaplan-Meier Analysis

Patients in dialysis facilities with a patient to nurse ratio of ≥3 and <4 had the lowest risk of suffering an IRH, while patients in facilities with a patient to nurse ratio of <3 or ≥4 had a higher risk of suffering an IRH with nearly identical survival curves, shown in Figure 2. Patients with an unknown patient to nurse ratio had an IRH risk somewhere in the middle.

A log-rank test was performed to determine if the results were statistically significant. This resulted in a p-value of < 0.0001, indicating that the curves are significantly different from each other.

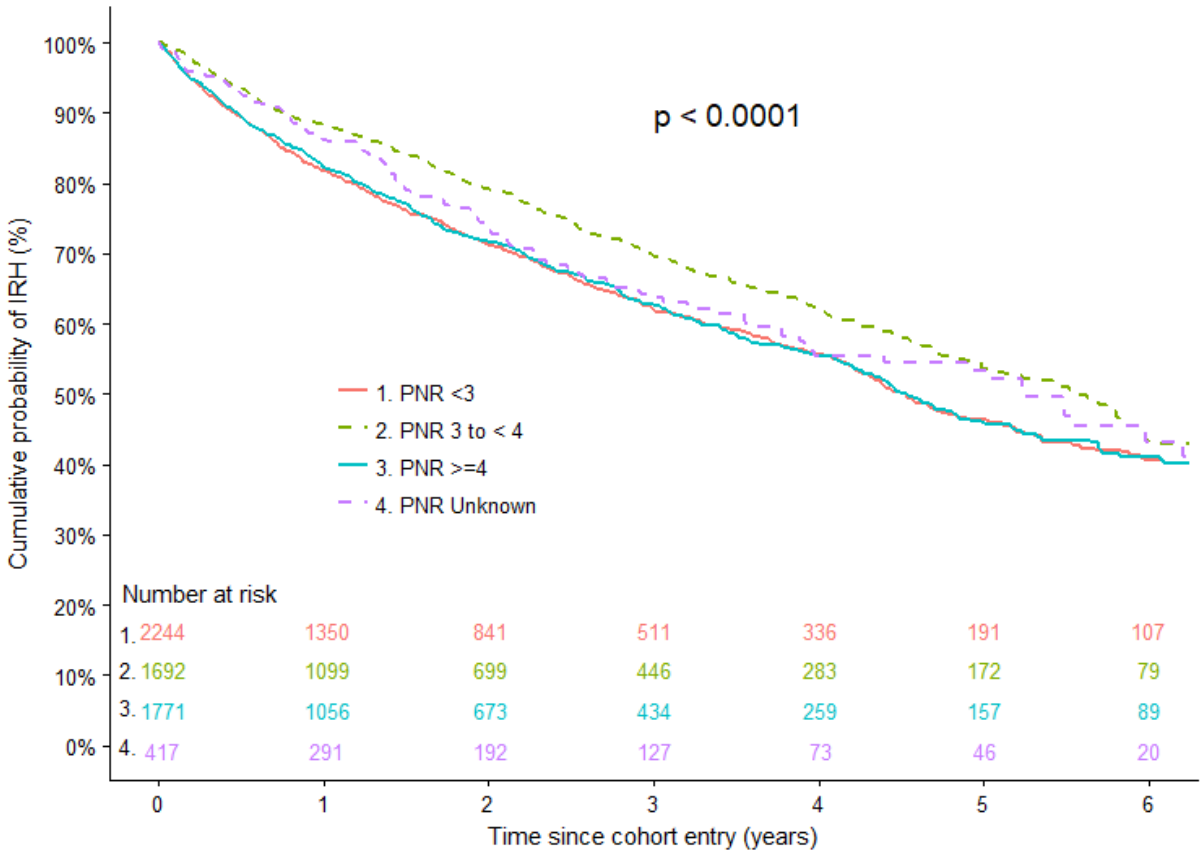

Figure 2. Unadjusted IRH-free Kaplan-Meier curves stratified by patient to nurse ratio (IRH, infection-related hospitalization)

Sensitivity Analysis

The results of the multiple sensitivity analyses are shown in Table 3. There are four sensitivity analyses on Table 3: one with the largest facility excluded, another with prevalent patients excluded, another with patients with follow-up in 2 or more facilities excluded and another with steroids included as a covariate (which only includes patients with RAMQ's drug insurance). Hemodialysis patients sometimes chose to transfer from one facility to another, while others continued to undergo hemodialysis in the same facility during the entire follow-up. Only the patients who spent their entire follow-up receiving hemodialysis in the same facility (i.e. they never transferred to another facility) were included in the third sensitivity analysis.

If patients with follow-up in more than 2 facilities were excluded, the results of the sensitivity analysis were somewhat similar to those of the main analysis, but despite the changes in HR, the interpretation of the results remained the same.

However, the results from the second sensitivity analysis (where prevalent patients were excluded) differed somewhat from the main analysis. If prevalent patients were excluded, the results showed that a patient to nurse ratio of <3 was associated with a significantly increased risk of IRH, but the association between risk of IRH and a patient to nurse ratio of ≥4 disappeared.

The results were also somewhat different if the largest facility was excluded or if steroids are added to the model. If patients from the largest facility or patients without RAMQ's insurance plan were excluded (adjusted mixed effects Cox model with steroids), then the association between patient to nurse ratio and IRH was no longer statistically significant for any of the 3 strata.

Parameter	Adjusted Mixed Effects Cox Model				
	Main Analysis: Model without steroids (n=6124)	**Largest facility excluded**	**Prevalent patients excluded**	**Patients with follow-up in more than 2 facilities excluded**	**Model with steroids (n=4793)**
	HR (95%CI)				
Mean Patient to Nurse Ratio					
Less than 3 (<3)	1.12 (0.83, 1.51)	1.00 (0.87, 1.15)	1.36 (1.01, 1.82)	0.85 (0.54, 1.34)	1.10 (0.84, 1.43)
3 to less than 4 (3 to <4)			Reference		
More than 4 (4≤)	0.72 (0.55, 0.95)	0.99 (0.85, 1.15)	1.00 (0.75, 1.34)	0.56 (0.39, 0.80)	0.90 (0.70, 1.16)
Unknown	0.97 (0.61, 1.53)	0.94 (0.75, 1.16)	1.22 (0.79, 1.90)	1.00 (1.00, 1.01)	1.00 (0.66, 1.51)

HR, hazard ratio; CI, confidence interval

Table 3. Sensitivity Analysis: Mixed effects Cox models for first IRH

If the largest facility was excluded from the Kaplan Meier analysis, the association between patient to nurse ratio and risk of IRH disappeared entirely. As shown in Figure 3, all 4 of the Kaplan-Meier curves became very similar. A log rank test was done, resulting in a p-value of 0.59, indicating that the curves were not significantly different from each other.

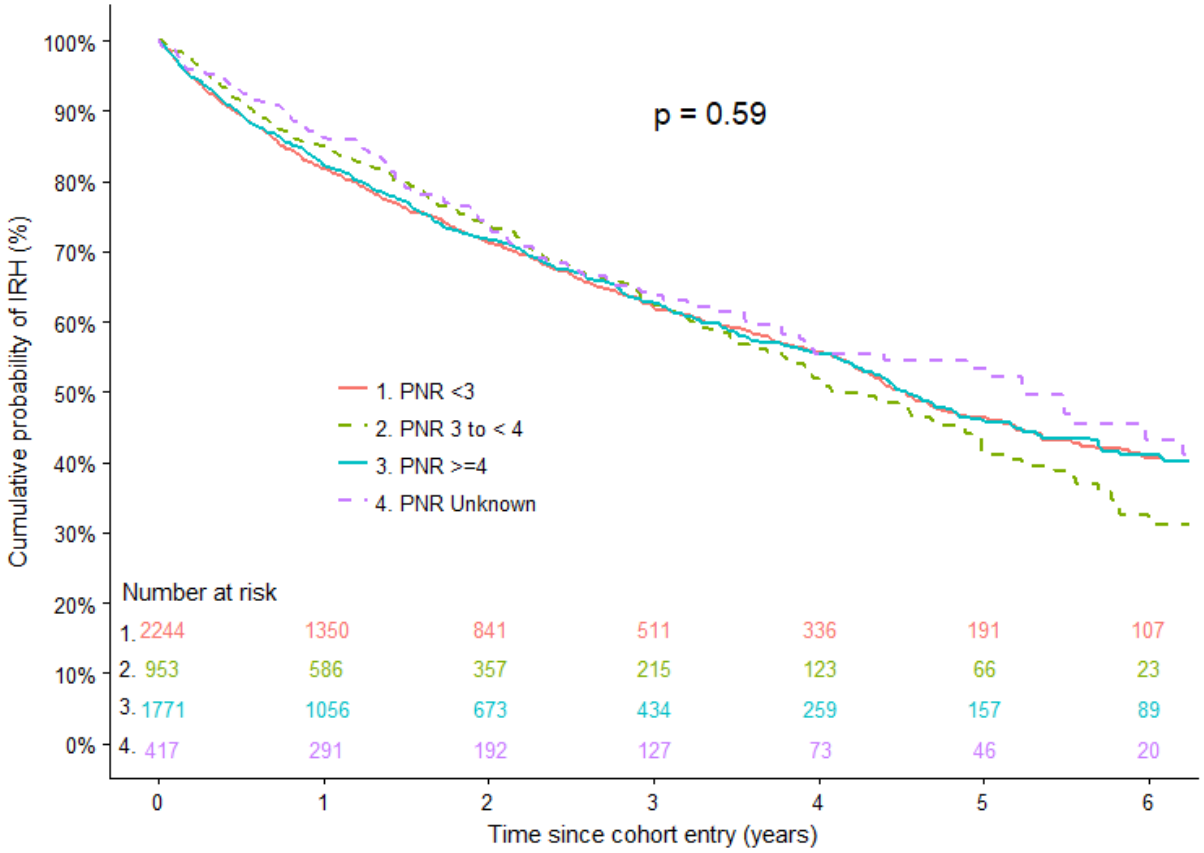

Figure 3. Sensitivity analysis: Unadjusted IRH-free Kaplan-Meier curves stratified by patient to nurse ratio (IRH, infection-related hospitalization; PNR, patient to nurse ratio)

.

Discussion

Summary of Results

Our adjusted mixed effects Cox model showed that that having a patient to nurse ratio of ≥4 was associated with a reduced risk of IRH and that a patient to nurse ratio of <3 is not associated with a significantly increased or decreased rate of IRH compared with those with a patient to nurse ratio of ≥3 and <4. However, our Kaplan Meier results showed that patients in facilities with a patient to nurse ratio of ≥3 and <4 have the lowest risk of suffering their first IRH, while those with a patient to nurse ratio of <3 or ≥4 have a higher risk of suffering their first IRH.

The overall incidence of IRH across all participating facilities was 0.193 IRH per patient year (95% CI: 0.187, 0.200). There was a substantial variation in IRH rates across each facility in this study. However, according to our results, this variation in IRH depending on the facility cannot be explained by patient to nurse ratio. There is likely something else that influences the IRH rates across different facilities.

Our results changed slightly once certain sensitivity analyses were done. Having a patient to nurse ratio of <3 was associated with an increased risk of IRH and a patient to nurse ratio of ≥4 was no longer associated with a reduced risk of IRH if prevalent patients were excluded. If the largest facility was excluded or if steroids were added to the model as a covariate, the association between risk of IRH and patient to nurse ratio disappeared entirely. The results of these sensitivity analyses may be a hint that the association between infection and patient to nurse ratio is more complicated than simple cause and effect, and that it is affected by multiple variables.

Interpretation

The majority of studies related to nurse staffing have found that a higher patient to nurse ratio (or a lower nurse to patient ratio)[234, 238, 243, 244] and lower nurse staffing in general[237, 243, 245-247] is associated with increased rates of infection. Studies also suggest that higher patient to nurse ratios or understaffing are associated with lower hand hygiene compliance,[248] higher infection transmission rates,[245] higher mortality[231, 249] and increased risk for surgical complications.[235,

[236, 250, 251] West et al.[225] found that a higher number of nurses per bed was associated with higher survival, while higher workload was associated with higher mortality. Arenas et al.[248] analyzed hand hygiene practices in nine Spanish hemodialysis units and found that poor compliance was associated with a higher patient to nurse ratio, hemodialysis units running three scheduled shifts of dialysis per day and chronic hemodialysis units (compared to acute hemodialysis units).

Our results do not reflect those findings, as IRH rates seem to have a non-monotonic association with patient to nurse ratio in this population. However, these findings are not unprecedented. Reviews in the past have noted that while there is a general trend, the results of studies related to nurse staffing have been varied, and not all studies find an association between nurse staffing and patient outcomes or infection rates.[223, 230]

It should be noted that these studies are also very heterogeneous, with different methods, sample sizes, patient populations, etc. Some studies focus on pediatric patients, others on intensive care unit (ICU) patients, others on the neonatal intensive care unit (NICU) patients, and others on patients undergoing various types of surgery. Some are multi-centre, others are not, and many studies use other measures of nurse staffing or workload besides patient to nurse ratio. As a result, this raises issues with comparability and generalizability, especially since we are not aware of any other study that has examined the association between infection and patient to nurse ratio in the hemodialysis patient population.

Whitman et al.[252] found no association between central line infections and nurse staffing across various specialty units, but noted that the impact of nurse staffing on other outcomes did vary among specialty units. For example, they found an inverse association between nurse staffing and medication errors in cardiac and non-cardiac intensive care units and between staffing and falls in cardiac intensive care. This implies that lower nurse staffing may affect different specialty units in different ways, and not necessarily in terms of infection rates.

West et al.[225] found a significant interaction between the number of nurses and ICU mortality, but no significant interaction was found between the number of nurses and hospital mortality. Their results show that the impact of nurse staffing was highest in the ICU, on patients at the

greatest risk of death. This also suggests that the importance of nurse surveillance is the key mechanism that links nurse staffing to patient outcomes in the ICU.

California is noted to have (on average) 12 patients for every dialysis nurse, yet patient outcomes in California are among the best in the United States despite the lack of mandated staffing ratios. This implies that there are other factors that affect patient outcomes other than patient to nurse ratio. One aspect of hemodialysis care is the long term relationship between the health care team and the patients, as several patients are cared for in the same room with the nurses nearby. It is possible that these interpersonal relationships between patients and the health care team may affect patient outcomes.[253]

Hugonnet et al.[254] have noted in their review that the relationship between understaffing, patient overcrowding and nosocomial infection is not a linear cause-effect relationship. It is likely due to the interaction of several factors with synergistic effects, and determining them may be difficult due to various methodological shortcomings.

Thus, it is possible that the lack of obvious monotonic association between patient to nurse ratio and infection in the dialysis patient population may be because nurse surveillance is less important in dialysis facilities. It is also likely that there may be other factors (or a combination of factors) that influence the IRH rates in the dialysis population besides patient to nurse ratio. Elucidating these factors in relation to nurse staffing would require more detailed studies.

Strengths and Weaknesses of this study

One strength of our study is its large sample size and high statistical power, as it includes 21 dialysis centers across Quebec and linked data from RAMQ and Med-Echo. RAMQ provides free healthcare insurance to all residents of Quebec (except those with private insurance), and the majority of dialysis facilities in the province have agreed to participate in this study, allowing us to include most dialysis patients in Quebec.

Another strength is that this study includes a balanced blend of existing data and measurement of new variables that are not normally included in existing databases. In this case, the variable of interest is patient to nurse ratio, with multiple measurements taken to account for seasonal variations.

However, our study does have some limitations. As this is an observational study, our ability to make any causal claims is very limited. We can only determine associations between different variables. The best way to test causality would be a clinical trial, but it may not be feasible or ethical.

One source of information bias is that, despite our efforts, some facilities were lost to follow-up in terms of measuring the patient to nurse ratio. Thus, for some facilities in this study, we were not able to obtain all three measurements to calculate the mean patient to ratio over time and to account for seasonal changes.

Other sources of information bias include the fact that the mean patient to nurse ratio was used for each center. Given that some facilities have multiple rooms devoted to hemodialysis sessions, there could be variations within the same dialysis facility depending on the room and the time of day. It is also possible that satellite and semi-autonomous hemodialysis units may include patients at lower risk of infection and have a higher patient to nurse ratio, which would bias the results. However, this cannot completely explain our results as large in-center facilities without semi-autonomous units had high patient to nurse ratios.

It should also be noted that our values of patient to nurse ratio are fairly homogenous in that the range is not that high. The lowest patient to nurse ratio was about 1.6 and the highest was measured at about 4.6. As a result, we cannot really conclude if a patient to nurse ratio of 4 or more is really associated with an increased risk of IRH in the context of this study. It is possible that, in the hemodialysis population, we may only see increased risk of IRH in dialysis facilities with much higher patient to nurse ratios.

Another limitation of this study was that we were unable to obtain data from the Canadian Organ Replacement Register (CORR), a national database that tracks dialysis activity, vital organ transplantation, organ donation and wait list statistics in Canada. Data from CORR would have included some variables not available from Med-Echo and the RAMQ, such as the patient's vascular access (AVF, AVG or CVC) and their laboratory results (such as serum albumin, estimated glomerular filtration rate (eGFR), hemoglobin, creatinine, phosphorous, urea, etc.). These variables are possible risk factors for IRH that we could not adjust for in our model in this study. Their association with infection has been shown in various studies and disputed in others.

Many studies have shown that a patient's vascular access has a considerable impact on their risk of suffering an infection, with patients using a CVC being the most vulnerable.[23-27] Results concerning laboratory results are somewhat mixed. One study found that a higher phosphorous level was associated with increased risk of IRH, but not albumin, eGFR, urea or hemoglobin.[242] However, another study suggested that low albumin increased the risk of septicemia among dialysis patients,[209] two other studies found that low albumin was associated with higher infection severity[208, 255] and another study found that lower serum albumin was associated with a higher risk of infection-related events (in older patients).[256] Among older patients with chronic kidney disease, lower eGFR (and thus, lower kidney function) was associated with a higher risk of IRH[257] and bloodstream infections.[258] Lower serum creatinine, lower serum albumin and lower BMI have been associated with higher mortality.[259, 260] Lower hemoglobin has been associated with increased risk of bacteremia[261] and vascular access infection.[262] However, other studies have found a non-monotonic[256] or non-existent[263] association between hemoglobin and infection.

It should also be noted that information relating to vaccinations, topical antibiotics, or antibiotic locks administered to participating hemodialysis patients was not available in both databases used in this study, despite the amount of research done on these subjects. Information relating to *S. aureus* nasal carriers was also unavailable in both databases used in this study. We also could not determine if there was an association between patient to nurse ratio or prior IRH and access-related infections as we did not have the necessary data to perform these analyses. This was why we were unable to adjust for these variables in this study.

It should also be noted that we use various codes to determine whether the patient is on chronic hemodialysis, if they have suffered an IRH (and what type) and their comorbidities. We only know what has been written down, and thus the specificity and the sensitivity of our data is not perfect. Notably, these codes do not measure disease severity and do not include infections that don't require hospitalization. As a result, there may be some residual confounders present in our study.

Another limitation is that, for prevalent patients, we cannot know if that comorbidity is a cause or consequence of hemodialysis. This is especially true for some comorbidities like hypertension, which can cause ESRD or be a consequence of it.

While our study does include most dialysis patients in Quebec, our results may not be generalizable to all facilities. There is a considerable variation in patient to nurse ratios and IRH rates across different facilities, and not including all of them (especially the larger ones) could have affected our results.

Conclusion

The goal of this study was to elucidate the association between patient to nurse ratio and IRH in the chronic hemodialysis patient population. Our analysis, using data from both RAMQ and Med-Echo, allows us to conclude that the association between patient to nurse ratio and IRH is unclear, especially as our results seem to be different after certain sensitivity analyses are done.

It appears that there is something else influencing IRH rates across different facilities besides patient to nurse ratio. More studies would be required to determine what factors are responsible for the varying IRH rates across different facilities.

Article 2: The Association Between Alcohol-Based Hand Rub Dispensers and Hand-Washing Stations and Infection-Related Hospitalizations in Hemodialysis Patients

Elaine Mong-Slezak,[1] Émilie René,[1] Naoual Elftouh,[1] Jean-Philippe Lafrance[1, 2, 3]

1 Maisonneuve-Rosemont Hospital Research Center, Montreal, Canada

2 Department of Pharmacology and Physiology, University of Montreal, Montreal, Canada

3 Division of Nephrology, Maisonneuve-Rosemont Hospital, 5415, boul. de l'Assomption, Montreal, QC H1T 2M4 Canada

Introduction

The human skin is a complex organ that regulates our interactions with the outside world. It is also a complex ecosystem that supports diverse communities of microorganisms.[264, 265] These microorganisms include transient visitors that do not normally multiply or grow on the skin, as well as permanent residents that make up the normal skin flora.[265] Resident skin flora reside in the deeper areas of the skin and are resistant to removal, while transient flora colonize the superficial layers of the skin and are easier to remove by hand washing. Transient skin flora are the organisms that are most frequently associated with hospital-related infections. They are frequently acquired by healthcare workers via direct contact with patients and contaminated surfaces.[266] It is well known that increased adherence to proper hand hygiene practices reduces the transmission of transient microorganisms associated with disease, resulting in reduced incidence of nosocomial infections.[266-269]

Hand hygiene remains a cornerstone for the prevention of nosocomial infection, even among dialysis patients.[133, 144] Unfortunately, hand hygiene compliance is low in many hospitals studied.[218, 270-272] Reasons cited include high workload and understaffing, antiseptic or antimicrobial agents causing skin irritation, inadequate knowledge of guidelines or protocols for hand hygiene, lack of role models, not recognizing the risk of cross-transmission of microbial pathogens and/or the lack of availability or inconvenient location of sinks.[267, 272]

It has been shown that putting alcohol-based hand rub dispensers (ABHRD) within direct line of sight when entering the room or seeing the patient improves compliance.[273, 274] Thomas et al. found that greater quantities of alcohol-based hand rub (ABHR) products were used when the dispensers were in greater proximity to the patients and in a more conspicuous location. However, the number of ABHRD available had no effect on daily ABHR product consumption.[275] Studies have also shown that fewer sinks or inconvenient location of sinks are associated with reduced hand-washing compliance and greater incidence of *Clostridium difficile* infections.[276-278] No similar studies have been done in the hemodialysis population. Thus, the purpose of this study is to evaluate if a higher availability and proximity of handwashing stations and ABHRD is associated with lower rates of infection-related hospitalizations (IRH) in patients receiving chronic hemodialysis.

Patients and Methods

Study Design

This study was a retrospective cohort study involving both incident and prevalent chronic hemodialysis patients. Data at the patient level was extracted from the RAMQ and Med-Echo databases described below. All databases were linked by RAMQ. Facility level space factors at the 21 participating centers were determined by direct measurement.

Databases

Régie de l'assurance maladie du Québec (RAMQ)

The RAMQ is the universal health care public insurance agency in Quebec, providing a Health Insurance Card which allows free access to medical services for all Quebec residents. It covers all dialysis treatments and transplant surgeries in Quebec, with notable exceptions being military personnel and First Nations. The RAMQ's registration files of insured people include demographic information such as age, sex, type of medication insurance plan, postal code, etc. It also has a physician claims database that provides information on medical services provided, diagnosis and reimbursements. The RAMQ also provides medication services to all Quebec residents who are 65 or older, younger residents (less than 65 years of age) who are on social assistance and Quebec residents who are not covered by private insurance. Thus, it can also provide information on all dispensed prescriptions and reimbursements for said prescriptions.

Québec hospital discharge summary database (Med-Echo)

Med-Echo is a database that collects data from discharge abstracts of all hospitalizations within Quebec. It provides clinical and administrative data relating to physical and mental health. Med-Echo is owned and managed by the Department of Health and Social Services. Its data is stored in RAMQ's facilities. It includes data on diagnosis (using ICD-10 codes since 2006), procedures performed within the hospital, admission and discharge dates and in-hospital mortality.

Study Population

This study involved chronic hemodialysis patients, both incident and prevalent, from January 1, 2007 to March 31, 2013 at 21 participating dialysis facilities. All patients must have been at least 18 years of age or older at the date of dialysis initiation and must have been undergoing dialysis for at least 90 days. The date of cohort entry for this study was defined as the date of dialysis initiation for incident dialysis patients and January 1, 2007 for prevalent patients.

First, all dialysis diagnostics, billings and procedures were identified between October 1, 2006 and 31 March, 2013 and the number of dialysis services were counted for each patient. The codes used for this study can be found in Table 13 in Appendix I.

Patients who received a transplant prior to starting dialysis were also were excluded by finding kidney transplant-related diagnostics, billings and procedures prior to the first dialysis code in the study period. Transplant recipients were excluded as they tend to experience better survival rates and suffer different types of infections compared to hemodialysis patients.[63]

Dialysis may be done for either a short or long period of time (for acute or chronic renal failure), but only chronic hemodialysis patients were included in this study. To ensure that all patients in the final cohort were undergoing chronic hemodialysis, an algorithm was used to select all dialysis codes in a 90-day window for each given dialysis code. This algorithm evaluates three criteria to validate whether a patient is on chronic hemodialysis and for how long:

1) ≥ 3 in-center hemodialysis codes between day 75 and 90
2) Or ≥ 2 satellite dialysis codes between day 0 and 90
3) Or 1 satellite hemodialysis supervision dialysis code between day 60 and 90

This algorithm is first applied to the date of entry into the cohort (first dialysis session) and chronologically for each dialysis code afterward. If a patient has less than 90 days of follow-up or no dialysis code after 90 days of follow-up, they were excluded. In Quebec, billings are handled differently between in-center hemodialysis and satellite units. In-center hemodialysis treatments are billed by the attending nephrologist (one code for each patient per treatment).

Individual treatments in satellite units cannot be billed, but the attending nephrologist bills once a month for the supervision of the unit (one code for each patient per month).

All patients who were not receiving chronic hemodialysis were excluded. This includes:

- Patients whose follow-up ended before January 1 2007
- Patients with less than 3 months of follow-up after cohort entry
- Patients not satisfying the dialysis algorithm above

The patients' modality was assessed in the 90 days after cohort entry, with those with more than 3 hemodialysis codes between day 75 and 90 being considered as being on hemodialysis. If this was not the case, then the modality of their last dialysis code in the 90 days after cohort entry is considered to be their modality. Only those undergoing hemodialysis at a hospital or satellite centre were included in the study. Patients undergoing peritoneal dialysis or home hemodialysis were excluded, as infection rates and types vary greatly by modality,[242] and because home dialysis is done at home or work rather than a dialysis unit.

In the case where a patient switches modality to peritoneal dialysis or home hemodialysis, the last date of follow-up is the date of modality transfer. Follow-up is also stopped if there is a gap of at least 30 days (in a hospital) or 60 days (in a satellite center) between two hemodialysis services.

Each patient received hemodialysis at a certain facility, and while most chose to stay at the same facility throughout all their follow-up, some may have chosen to switch to another. If a patient had two consecutive dialysis services in another facility, then they were considered to have switched to that dialysis facility. Patients who did not have any period of hemodialysis in a participating facility were excluded from the study.

All patients included in the final cohort were followed from their date of dialysis initiation until the earliest date of modality transfer (to peritoneal dialysis or home hemodialysis), discontinuation of hemodialysis, death, kidney transplantation or until the end of the study period.

Outcome

Infection-related hospitalization

An infection-related hospitalization (IRH) is defined as a hospitalization in which an infection is the principal diagnosis. IRHs were classified in using ICD-10 codes (which can be found on Table 15 in Appendix I). IRH include many types of infections; in this study, it is categorized into abdominal infections, access-related infections, genitourinary infections, musculoskeletal infections, pneumonia, septicemia, skin and other infections.

Assessment of Facility-Level Variables

Assessment of facility-level variables was done by hand using a tape ruler at each participating centre. Both hand-washing stations and alcohol-based hand rub dispensers were assessed:

Hand-washing station and alcohol-based hand rub dispenser variables measured:

- Number of hand-washing stations or dispensers in the dialysis unit
- Mean distance in meters between each dialysis station and the nearest hand washing station or dispenser
- Hand-washing station/dispenser ratio (defined as the number of dialysis stations divided by the number of hand-washing stations or dispensers)

Mean distance of dialysis station to the nearest hand-washing station was categorized using the first, second and third quartiles: <4.75 m, 4.75 m to 6 m or >6 m.

Hand-washing station ratio was categorized using the first, second and third quartiles: <3.15, 3.15 to 3.75 or >3.75 m.

Mean distance of dialysis station to the nearest ABHRD was categorized using the first, second and third quartiles: <1.5 m, 1.5 m to 3 m or >3 m.

ABHRD ratio was categorized using the first, second and third quartiles: <0.8, 0.8 to <1.5 or ≥1.5.

If a patient suffers an IRH in a facility where the facility-based variables were unknown (i.e. in a non-participating centre), they end up in a ‘missing’ category. These patients were still part

of the cohort (as they have a period of follow-up in a participating facility), but the facility-level variables associated with their IRH were unknown as it is tied with the last dialysis facility they received services from. These patients were represented as the 'unknown' category in our analysis.

Multiple measurements of these facility-level variables were taken over time, allowing us to take into account any changes that might have happened over the course of the study. This is why it is possible for a facility to be associated with more than one value of a given facility-level variable.

Assessment of Covariates

Baseline patient characteristics assessed at cohort entry include age, sex and incident dialysis status (whether the patient is incident or prevalent).

Comorbidities were assessed two years before cohort entry and were identified with a combination of ICD-9 and ICD-10 codes from RAMQ data. The specific codes can be found on Table 14 in Appendix I.

Comorbidities assessed in this study include hospitalization in the prior year, hemodialysis incidence, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease, cirrhosis or chronic liver disease, congestive heart failure, diabetes, history of amputation, hyperlipidemia, hypertension, malignancy, peripheral vascular disease, valvular disease, prior IRH or steroid use.

Steroid use was assessed six months before cohort entry. We considered a person a steroid user if they had at least one prescription for it in the six months prior to cohort entry and were using RAMQ's drug insurance plan.

Statistical Analysis

Mean, standard deviation, median and interquartile range were used to describe continuous variables such as age and length of follow-up. Frequencies were used describe categorical variables such as comorbidities and drug use.

Incidence Rate

IRH incidence rates were calculated by dividing the total number of IRH by the total number of years of follow-up. In this study, it is presented as the IRH incidence rate per patient-year. The 95% confidence intervals (CI) were calculated using the Poisson Model.

Kaplan-Meier

The Kaplan-Meier analysis was used to determine infection-free survival curves and probability of survival. The log rank test was used to determine the difference between the four survival curves.

Mixed Effects Cox model

Conventional regression models assume that patients have the risk of suffering the event in question independently of one another. However, this is may not necessarily be true in multicentre studies like this one, where patients within the same 'cluster' (for example, a dialysis unit) are likely to have outcomes that are correlated with one another. This is especially true for this study since we focus on facility-level variables, which are the same for all patients receiving care in the same dialysis unit. This violates the assumption of independent events and prevents us from using a conventional regression model. Thus, we must use mixed effects (*hierarchical*) models to analyze multilevel data.

The study population may also be a heterogeneous in that there may be one or more subsets of the population that are more susceptible to the event of interest than others. These individuals with a higher risk of the event tend to experience it first, leaving behind the less susceptible (or healthier) individuals in the cohort. This may result in the population hazard appearing to decrease with time (due to the loss of the susceptible individuals from the cohort) even if the individual hazards are constant. This may result in the regression coefficients being underestimated if the heterogeneous population is left unaccounted for.

The *mixed effects Cox regression model* is an extended Cox model which can adjust for heterogeneity. It is a survival regression model that includes both fixed effects coefficients (which are constant within a given cluster) and random effects coefficients (which vary between individuals). Thus, this study uses mixed effects Cox model to take into account both

multilevel data and a heterogeneous population. We used a mixed effects Cox model in this study for the first IRH, including the facility as a random effect. In this case, the facility related variable is distance from the hand-washing station or alcohol-based hand rub dispenser to the nearest bed and the proportion of hand-washing stations or alcohol-based hand rub dispenser to the number of dialysis stations. Models were adjusted for all covariates listed above.

Sensitivity analyses

To test the robustness of our results, four different sensitivity analyses were performed for each facility-level variable. The first sensitivity analysis excluded the largest facility. This was to see if including this facility in our analysis affects our results. The second sensitivity analysis involved excluding all prevalent patients, leaving only incident patients in the cohort. The third sensitivity analysis excluded any patient with follow-up in more than one facility. This was done to test whether patients switching facilities affected our results.

While RAMQ's drug insurance plan was widely used in Quebec, there were those that were not covered by it or who used private insurance to pay for their medications. Thus, these patients were not included in RAMQ data, and their drug prescriptions were unknown to us. This was why steroid use was not included in the main analysis and why we decided to perform a fourth sensitivity analysis to see whether steroid use had any effect on our results.

In this case, the facility related variables are the number of hand-washing stations or dispensers in the dialysis unit, the hand-washing station/dispenser ratio and the mean and median distance in meters between each dialysis station and the nearest hand washing station or dispenser.

The analysis was done using SAS statistical software. Results were considered statistically significant if $P < 0.05$.

Results

Description of baseline characteristics

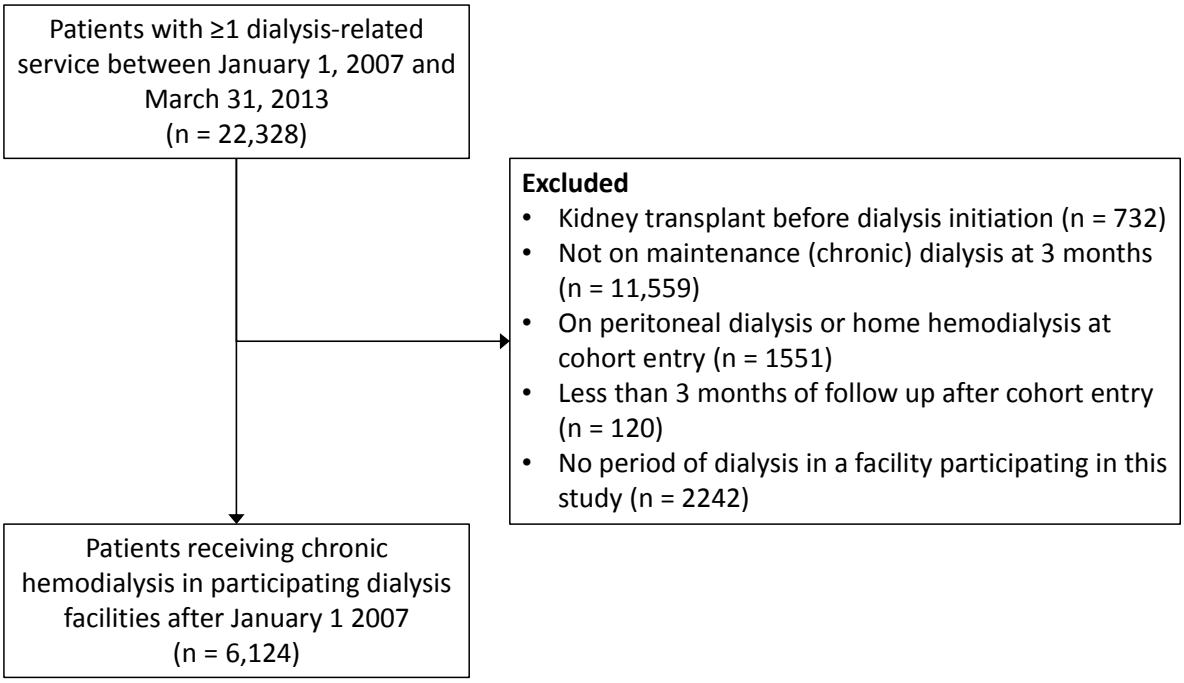

Figure 4. Summary of the construction of the cohort

This study included 6,124 chronic hemodialysis patients in 21 participating facilities in the final cohort. The reason why a large number of patients were excluded due to not being on maintenance (chronic) dialysis at three months was because we initially included every single patient with at least one dialysis-related code. This included patients requiring acute dialysis, patients that recovered and patients that died before three months of follow-up.

The cohort was stratified based on the mean distance of dialysis station to the nearest hand-washing station or alcohol-based hand rub dispenser (ABHRD) and based on the hand-washing station/dispenser ratio. The distribution can be seen in Tables 5 to 8.

7 facilities had a mean distance of dialysis station to the nearest hand-washing station of <4.75 m. 6 facilities had a mean distance of dialysis station to the nearest hand-washing station of 4.75 m to 6 m. 9 facilities had a mean distance of dialysis station to the nearest hand-washing station of >6 m.

8 facilities had a hand-washing station ratio of <3.15. 6 facilities had a hand-washing station ratio of 3.15 to 3.75. 8 facilities had a hand-washing station ratio of >3.75.

5 facilities had a mean distance of dialysis station to the nearest ABHRD of <1.5 m. 7 facilities had a mean distance of dialysis station to the nearest ABHRD of 1.5 m to 3 m. 10 facilities had a mean distance of dialysis station to the nearest ABHRD of > 3m.

5 facilities had a ABHRD ratio of <0.8. 12 facilities a ABHRD ratio of 0.8 to <1.5. 5 facilities had an ABHRD ratio of ≥1.5. In all cases, 417 (6.8%) patients had an unknown ABHRD ratio. Baseline characteristics are summarized in Table 5. The cohort in general had a median age of 68.7 years, with an interquartile range of 58.2-77.3. The median follow-up was 2.0 years with an interquartile range of 0.9-3.8 years. Neither age nor follow-up were normally distributed in this cohort, so median and interquartile range were given instead of mean and standard deviation. 39.9% of patients were female, 61.8% of them were incident patients and 19.7% of patients suffered an IRH prior to cohort entry. Diabetes, cardiovascular disease and hypertension were quite common, with 50.7% of patients suffering from diabetes, 48.0% from cardiovascular disease and 70.8% from hypertension.

For mean distance of dialysis station to hand-washing station/ABHRD and hand-washing station/ABHRD ratio, there were no statistically significant differences in gender distribution between the different strata. Age distribution was also very similar among the patients whose facility-level variables were known, although patients with unknown facility-level variables tended to be slightly younger. There were no statistically significant differences in the distribution of cerebrovascular disease, history of amputation and (in most cases) diabetes. However, there were many differences in the distribution of comorbidities between each stratum, as shown in Tables 4 to 7.

Covariates	Mean Distance of Dialysis Station to Hand-washing Station (m)					p-value
	All patients	<4.75	4.75 to 6	>6	Unknown**	
	n=6124 (%)	n=2052 (%)	n=1483 (%)	n=2172 (%)	n=417 (%)	
Age (years)*	68.7 (58.2-77.0)	67.7 (57.1-76.5)	71.3 (61.7-78.3)	68.8 (58.6-77.1)	64.9 (53.4-73.7)	<.0001
Sex (female)	2443 (39.9)	852 (41.5)	597 (40.3)	833 (38.4)	161 (38.6)	0.19
Hospitalization in prior year	3973 (64.9)	1269 (61.8)	949 (64.0)	1489 (68.6)	266 (63.8)	<.0001
Hemodialysis incidence	3786 (61.8)	1229 (59.9)	948 (63.9)	1327 (61.1)	282 (67.6)	0.006
Cardiovascular disease	2940 (48.0)	919 (44.8)	747 (50.4)	1119 (51.5)	155 (37.2)	<.0001
Cerebrovascular disease	429 (7.0)	150 (7.3)	99 (6.7)	156 (7.2)	24 (5.8)	0.65
Chronic pulmonary disease	1147 (18.7)	368 (17.9)	281 (19.0)	427 (19.7)	71 (17.0)	0.40
Cirrhosis or chronic liver disease	281 (4.6)	108 (5.3)	65 (4.4)	94 (4.3)	14 (3.4)	0.26
Congestive heart failure	1662 (27.1)	517 (25.2)	442 (29.8)	609 (28.0)	94 (22.5)	0.002
Diabetes	3104 (50.7)	1016 (49.5)	756 (51.0)	1138 (52.4)	194 (46.5)	0.09
History of amputation	144 (2.4)	54 (2.6)	32 (2.2)	48 (2.2)	10 (2.4)	0.77
Hyperlipidemia	3654 (59.7)	1193 (58.1)	896 (60.4)	1329 (61.2)	236 (56.6)	0.11
Hypertension	4338 (70.8)	1473 (71.8)	1087 (73.3)	1506 (69.3)	272 (65.2)	0.003
Malignancy	1070 (17.5)	343 (16.7)	278 (18.8)	388 (17.9)	61 (14.6)	0.17
Peripheral vascular disease	1497 (24.4)	429 (20.9)	399 (26.9)	543 (25.0)	126 (30.2)	<.0001
Valvular disease	695 (11.3)	231 (11.3)	177 (11.9)	254 (11.7)	33 (7.9)	0.13
Prior IRH	1207 (19.7)	407 (19.8)	320 (21.6)	413 (19.0)	67 (16.1)	0.06

* Median (IQR)

** Unknown mean distance of dialysis station to hand-washing station

IRH, infection-related hospitalization; IQR, interquartile range

Table 4. Baseline characteristics for mean distance of dialysis station to hand-washing station

Covariates	Ratio of Hand-washing Station to Dialysis Station					p-value
	All patients	<3.15	3.15 to 3.75	>3.75	Unknown**	
	n=6124 (%)	n=1687 (%)	n=2144 (%)	n=1876 (%)	n=417 (%)	
Age (years)*	68.7 (58.2-77.0)	67.5 (58.6-76.8)	68.9 (57.9-77.1)	70.0 (59.9-77.7)	64.9 (53.4-73.7)	<.0001
Sex (female)	2443 (39.9)	646 (38.3)	879 (41.0)	757 (40.4)	161 (38.6)	0.34
Hospitalization in prior year	3973 (64.9)	1076 (63.8)	1376 (64.2)	1255 (66.9)	266 (63.8)	0.18
Hemodialysis incidence	3786 (61.8)	1035 (61.4)	1301 (60.7)	1168 (62.3)	282 (67.6)	0.06
Cardiovascular disease	2940 (48.0)	832 (49.3)	1080 (50.4)	873 (46.5)	155 (37.2)	<.0001
Cerebrovascular disease	429 (7.0)	126 (7.5)	142 (6.6)	137 (7.3)	24 (5.8)	0.51
Chronic pulmonary disease	1147 (18.7)	338 (20.0)	359 (16.7)	379 (20.2)	71 (17.0)	0.01
Cirrhosis or chronic liver disease	281 (4.6)	98 (5.8)	100 (4.7)	69 (3.7)	14 (3.4)	0.01
Congestive heart failure	1662 (27.1)	471 (27.9)	571 (26.6)	526 (28.0)	94 (22.5)	0.11
Diabetes	3104 (50.7)	857 (50.8)	1099 (51.3)	954 (50.9)	194 (46.5)	0.36
History of amputation	144 (2.4)	42 (2.5)	43 (2.0)	49 (2.6)	10 (2.4)	0.61
Hyperlipidemia	3654 (59.7)	967 (57.3)	1241 (57.9)	1210 (64.5)	236 (56.6)	<.0001
Hypertension	4338 (70.8)	1245 (73.8)	1494 (69.7)	1327 (70.7)	272 (65.2)	0.002
Malignancy	1070 (17.5)	326 (19.3)	336 (15.7)	347 (18.5)	61 (14.6)	0.006
Peripheral vascular disease	1497 (24.4)	394 (23.4)	508 (23.7)	469 (25.0)	126 (30.2)	0.02
Valvular disease	695 (11.3)	192 (11.4)	222 (10.4)	248 (13.2)	33 (7.9)	0.004
Prior IRH	1207 (19.7)	331 (19.6)	405 (18.9)	404 (21.5)	67 (16.1)	0.04

* Mean (IQR)

** Unknown hand-washing station ratio

IRH, infection-related hospitalization; IQR, interquartile range

Table 5. Baseline characteristics for hand-washing station ratio

Covariates	Mean distance between dialysis station to ABHRD (m)					p-value
	All patients	<1.5	1.5 to 3	>3	Unknown**	
	n=6124 (%)	n=1981 (%)	n=2034 (%)	n=1692 (%)	n=417 (%)	
Age (years)*	68.7 (58.2-77.0)	69.3 (58.9-77.3)	68.6 (57.7-76.9)	69.1 (58.4-77.7)	64.9 (53.4-73.7)	<.0001
Sex (female)	2443 (39.9)	782 (39.5)	830 (40.8)	670 (39.6)	161 (38.6)	0.75
Hospitalization in prior year	3973 (64.9)	1292 (65.2)	1320 (64.9)	1095 (64.7)	266 (63.8)	0.95
Hemodialysis incidence	3786 (61.8)	1246 (62.9)	1205 (59.2)	1053 (62.2)	282 (67.6)	0.005
Cardiovascular disease	2940 (48.0)	1009 (50.9)	982 (48.3)	794 (46.9)	155 (37.2)	<.0001
Cerebrovascular disease	429 (7.0)	146 (7.4)	136 (6.7)	123 (7.3)	24 (5.8)	0.59
Chronic pulmonary disease	1147 (18.7)	373 (18.8)	365 (17.9)	338 (20.0)	71 (17.0)	0.34
Cirrhosis or chronic liver disease	281 (4.6)	85 (4.3)	96 (4.7)	86 (5.1)	14 (3.4)	0.41
Congestive heart failure	1662 (27.1)	562 (28.4)	516 (25.4)	490 (29.0)	94 (22.5)	0.007
Diabetes	3104 (50.7)	1015 (51.2)	1059 (52.1)	836 (49.4)	194 (46.5)	0.12
History of amputation	144 (2.4)	52 (2.6)	42 (2.1)	40 (2.4)	10 (2.4)	0.71
Hyperlipidemia	3654 (59.7)	1151 (58.1)	1284 (63.1)	983 (58.1)	236 (56.6)	0.001
Hypertension	4338 (70.8)	1411 (71.2)	1479 (72.7)	1176 (69.5)	272 (65.2)	0.01
Malignancy	1070 (17.5)	384 (19.4)	323 (15.9)	302 (17.9)	61 (14.6)	0.01
Peripheral vascular disease	1497 (24.4)	429 (21.7)	477 (23.5)	465 (27.5)	126 (30.2)	<.0001
Valvular disease	695 (11.3)	217 (11.0)	245 (12.1)	200 (11.8)	33 (7.9)	0.02
Prior IRH	1207 (19.7)	359 (18.1)	427 (21.0)	354 (20.9)	67 (16.1)	0.09

* Mean (IQR)

** Unknown mean distance between dialysis stration to ABHRD

ABHRD, alcohol-based hand rub dispenser;IRH, infection-related hospitalization; IQR, interquartile range

Table 6. Baseline characteristics for mean distance of dialysis station to ABHD

Covariates	ABHRD ratio					p-value
	All patients	<0.8	0.8 to <1.5	≥1.5	Unknown**	
	n=6124 (%)	n=1981 (%)	n=1877 (%)	n=1849 (%)	n=417 (%)	
Age (years)*	68.7 (58.2-77.0)	69.3 (59.4-77.3)	67.5 (57.5-76.2)	70.1 (59.5-78.0)	64.9 (53.4-73.7)	<.0001
Sex (female)	2443 (39.9)	777 (39.2)	721 (38.4)	784 (42.4)	161 (38.6)	0.07
Hospitalization in prior year	3973 (64.9)	1307 (66.0)	1237 (65.9)	1163 (62.9)	266 (63.8)	0.15
Hemodialysis incidence	3786 (61.8)	1251 (63.2)	1142 (60.8)	1111 (60.1)	282 (67.6)	0.01
Cardiovascular disease	2940 (48.0)	1068 (53.9)	848 (45.2)	869 (47.0)	155 (37.2)	<.0001
Cerebrovascular disease	429 (7.0)	147 (7.4)	131 (7.0)	127 (6.9)	24 (5.8)	0.66
Chronic pulmonary disease	1147 (18.7)	365 (18.4)	395 (21.0)	316 (17.1)	71 (17.0)	0.01
Cirrhosis or chronic liver disease	281 (4.6)	90 (4.5)	103 (5.5)	74 (4.0)	14 (3.4)	0.09
Congestive heart failure	1662 (27.1)	590 (29.8)	474 (25.3)	504 (27.3)	94 (22.5)	0.002
Diabetes	3104 (50.7)	1055 (53.3)	908 (48.4)	947 (51.2)	194 (46.5)	0.006
History of amputation	144 (2.4)	50 (2.5)	45 (2.4)	39 (2.1)	10 (2.4)	0.86
Hyperlipidemia	3654 (59.7)	1160 (58.6)	1135 (60.5)	1123 (60.7)	236 (56.6)	0.26
Hypertension	4338 (70.8)	1423 (71.8)	1337 (71.2)	1306 (70.6)	272 (65.2)	0.06
Malignancy	1070 (17.5)	390 (19.7)	322 (17.2)	297 (16.1)	61 (14.6)	0.008
Peripheral vascular disease	1497 (24.4)	415 (21.0)	498 (26.5)	458 (24.8)	126 (30.2)	<.0001
Valvular disease	695 (11.3)	216 (10.9)	220 (11.7)	226 (12.2)	33 (7.9)	0.07
Prior IRH	1207 (19.7)	359 (18.1)	401 (21.4)	380 (20.6)	67 (16.1)	0.01

* Mean (IQR)

** Unknown hand-washing station ratio

ABHRD, alcohol-based hand rub dispenser;IRH, infection-related hospitalization; IQR, interquartile range

Table 7. Baseline characteristics for ABHRD ratio

Hand-washing station and ABHRD Results

A hierarchical mixed effects Cox model was made for each facility-level variable to analyze whether they were associated with a greater or lesser risk of IRH (Tables 8 to 11). Given that these facility-level variables were stratified based on quartiles, the middle quartile was chosen as the reference point for most of the variables due to it being the most conservative reference point. We would be less likely to witness significant differences between the different strata, but any significant differences found would be more likely to be real.

For the first model, as shown in Table 8, a mean distance of dialysis station to hand-washing station of <4.75m was used as reference. A mean distance of dialysis station to hand-washing station of 4.75m to 6m was associated with an increased risk of IRH. However, there was no statistically significant association between IRH and a mean distance of dialysis station to hand-washing station of >6m.

Covariates	Mixed Effects Cox Model	
	Unadjusted HR	Adjusted HR
	HR (95% CI)	
Mean distance of dialysis station to hand-washing station		
Less than 4.75m (<4.75m)	Reference	
4.75m to 6m	1.33 (1.04, 1.70)	1.30 (1.03, 1.64)
More than 6m (>6m)	1.14 (0.91, 1.42)	1.13 (0.92, 1.40)
Unknown	1.08 (0.77, 1.52)	1.13 (0.82, 1.58)
Age (years)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Sex (female)	0.96 (0.87, 1.05)	0.96 (0.88, 1.06)
Hemodialysis incidence	1.46 (1.32, 1.61)	1.12(1.01, 1.23)
Hospitalization in prior year	1.10 (1.00, 1.21)	1.19 (1.07, 1.34)
Cardiovascular disease	1.27 (1.16, 1.39)	0.99 (0.88, 1.10)
Cerebrovascular disease	1.49 (1.28, 1.74)	1.18 (1.00, 1.39)
Chronic pulmonary disease	1.90 (1.71, 2.11)	1.58 (1.41, 1.77)
Cirrhosis or chronic liver disease	1.44 (1.18, 1.77)	1.18 (0.97, 1.45)
Congestive heart failure	1.41 (1.27, 1.55)	1.10 (0.98, 1.23)
Diabetes	1.29 (1.17, 1.41)	1.08 (0.97, 1.19)
History of amputation	1.80 (1.39, 2.32)	1.38 (1.05, 1.81)
Hyperlipidemia	1.15 (1.05, 1.27)	1.04 (0.94, 1.15)
Hypertension	1.26 (1.13, 1.40)	0.90 (0.80, 1.01)
Malignancy	1.24 (1.10, 1.39)	1.13 (1.00, 1.27)
Peripheral vascular disease	1.36 (1.23, 1.51)	1.05 (0.93, 1.18)
Valvular disease	1.24 (1.08, 1.43)	1.00 (0.87, 1.16)
Prior IRH	1.97 (1.78, 2.19)	1.66 (1.49, 1.85)

HR, hazard ratio; CI, confidence interval; IRH, infection-related hospitalization

Table 8. Mixed effects Cox model for first IRH (mean distance from dialysis station to hand-washing station)

For the second model, a hand-washing station ratio of 3.15 to 3.75 was used as reference. A hand-washing station ratio of <3.15 was associated with a significantly higher risk of IRH. However, there was no statistically significant association between a hand-washing station ratio of >3.75 and IRH.

Covariates	Mixed Effects Cox Model	
	Unadjusted HR	Adjusted HR
	HR (95% CI)	
Hand-washing station ratio		
Less than 3.15 (<3.15)	1.41 (1.09, 1.81)	1.38 (1.08, 1.58)
3.15 to 3.75	Reference	
More than 3.75 (>3.75)	1.22 (0.95, 1.57)	1.19 (0.93, 1.51)
Unknown	1.16 (0.80, 1.68)	1.20 (0.84, 1.72)
Age (years)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Sex (female)	0.96 (0.87, 1.05)	0.97 (0.88, 1.06)
Hemodialysis incidence	1.46 (1.32, 1.61)	1.12 (1.02, 1.24)
Hospitalization in prior year	1.10 (1.00, 1.21)	1.19 (1.07, 1.34)
Cardiovascular disease	1.27 (1.16, 1.39)	0.99 (0.89, 1.10)
Cerebrovascular disease	1.49 (1.28, 1.74)	1.18 (1.00, 1.39)
Chronic pulmonary disease	1.90 (1.71, 2.11)	1.57 (1.40, 1.76)
Cirrhosis or chronic liver disease	1.44 (1.18, 1.77)	1.18 (0.96, 1.45)
Congestive heart failure	1.41 (1.27, 1.55)	1.10 (0.98, 1.23)
Diabetes	1.29 (1.17, 1.41)	1.08 (0.98, 1.20)
History of amputation	1.80 (1.39, 2.32)	1.39 (1.06, 1.82)
Hyperlipidemia	1.15 (1.05, 1.27)	1.04 (0.94, 1.15)
Hypertension	1.26 (1.13, 1.40)	0.90 (0.80, 1.01)
Malignancy	1.24 (1.10, 1.39)	1.12 (0.99, 1.26)
Peripheral vascular disease	1.36 (1.23, 1.51)	1.05 (0.93, 1.18)
Valvular disease	1.24 (1.08, 1.43)	1.00 (0.86, 1.15)
Prior IRH	1.97 (1.78, 2.19)	1.67 (1.49, 1.86)

HR, hazard ratio; CI, confidence interval; IRH, infection-related hospitalization

Table 9. Mixed effects Cox model for first IRH (hand-washing station ratio)

For the third model, a mean distance between dialysis station to ABHRD of 1.5 m to 3 m was used as reference. There was no statistically significant association between mean distance between dialysis station to ABHRD and IRH.

Covariates	Mixed Effects Cox Model	
	Unadjusted HR	Adjusted HR
	HR (95% CI)	
Mean distance between dialysis station to ABHRD		
Less than 1.5m (<1.5m)	1.13 (0.86, 1.49)	1.14 (0.88, 1.48)
1.5m to 3m	Reference	
More than 3m (>3m)	1.14 (0.89, 1.46)	1.13 (0.89, 1.43)
Unknown	1.04 (0.72, 1.51)	1.10 (0.77, 1.57)
Age (years)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Sex (female)	0.96 (0.87, 1.05)	0.97 (0.88, 1.06)
Hemodialysis incidence	1.46 (1.32, 1.61)	1.12 (1.02, 1.23)
Hospitalization in prior year	1.10 (1.00, 1.21)	1.19 (1.07, 1.34)
Cardiovascular disease	1.27 (1.16, 1.39)	0.99 (0.89, 1.10)
Cerebrovascular disease	1.49 (1.28, 1.74)	1.18 (1.00, 1.39)
Chronic pulmonary disease	1.90 (1.71, 2.11)	1.58 (1.41, 1.76)
Cirrhosis or chronic liver disease	1.44 (1.18, 1.77)	1.18 (0.96, 1.45)
Congestive heart failure	1.41 (1.27, 1.55)	1.10 (0.98, 1.23)
Diabetes	1.29 (1.17, 1.41)	1.08 (0.98, 1.19)
History of amputation	1.80 (1.39, 2.32)	1.38 (1.05, 1.81)
Hyperlipidemia	1.15 (1.05, 1.27)	1.04 (0.94, 1.15)
Hypertension	1.26 (1.13, 1.40)	0.90 (0.80, 1.01)
Malignancy	1.24 (1.10, 1.39)	1.12 (1.00, 1.26)
Peripheral vascular disease	1.36 (1.23, 1.51)	1.05 (0.93, 1.18)
Valvular disease	1.24 (1.08, 1.43)	1.00 (0.87, 1.16)
Prior IRH	1.97 (1.78, 2.19)	1.67 (1.49, 1.86)

HR, hazard ratio; CI, confidence interval; ABHRD, alcohol-based hand rub dispenser; IRH, infection-related hospitalization

Table 10. Mixed effects Cox model for first IRH (Mean distance from dialysis station to ABHRD)

For the fourth model, an ABHRD ratio of 0.8 to <1.5 was used as reference. An ABHRD ratio of ≥1.5 was associated with a significantly lower risk of IRH. However, there was no statistically significant association between an ABHRD ratio of <0.8 and IRH.

Covariates	Mixed Effects Cox Model	
	Unadjusted HR	Adjusted HR
	HR (95% CI)	
ABHRD ratio		
Less than 0.8 (<0.8)	1.00 (0.83, 1.22)	1.02 (0.81, 1.28)
0.8 to less than 1.5 (0.8 to <1.5)	Reference	
1.5 or more (≥1.5)	0.78 (0.64, 0.95)	0.76 (0.60, 0.95)
Unknown	0.89 (0.67, 1.19)	0.95 (0.68, 1.32)
Age (years)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Sex (female)	0.96 (0.87, 1.05)	0.97 (0.88, 1.06)
Hemodialysis incidence	1.46 (1.32, 1.61)	1.12 (1.02, 1.23)
Hospitalization in prior year	1.10 (1.00, 1.21)	1.19 (1.07, 1.33)
Cardiovascular disease	1.27 (1.16, 1.39)	0.99 (0.89, 1.10)
Cerebrovascular disease	1.49 (1.28, 1.74)	1.18 (1.00, 1.39)
Chronic pulmonary disease	1.90 (1.71, 2.11)	1.57 (1.40, 1.76)
Cirrhosis or chronic liver disease	1.44 (1.18, 1.77)	1.18 (0.96, 1.45)
Congestive heart failure	1.41 (1.27, 1.55)	1.10 (0.98, 1.23)
Diabetes	1.29 (1.17, 1.41)	1.08 (0.98, 1.20)
History of amputation	1.80 (1.39, 2.32)	1.38 (1.05, 1.82)
Hyperlipidemia	1.15 (1.05, 1.27)	1.04 (0.94, 1.15)
Hypertension	1.26 (1.13, 1.40)	0.90 (0.80, 1.01)
Malignancy	1.24 (1.10, 1.39)	1.12 (1.00, 1.26)
Peripheral vascular disease	1.36 (1.23, 1.51)	1.05 (0.93, 1.18)
Valvular disease	1.24 (1.08, 1.43)	1.00 (0.87, 1.16)
Prior IRH	1.97 (1.78, 2.19)	1.67 (1.50, 1.87)

HR, hazard ratio; CI, confidence interval; ABHRD, alcohol-based hand rub dispenser; IRH, infection-related hospitalization

Table 11. Mixed effects Cox model for first IRH (ABHRD ratio)

Kaplan-Meier Analysis

A Kaplan-Meier analysis was used to estimate a survival curve for time to first infection-related hospitalization as well as the patients' survival rate in each group, stratified based on mean distance of dialysis station to the nearest hand-washing station/ABHRD and hand-washing station/ABHRD ratio.

Patients in dialysis facilities with a mean distance of dialysis station to the nearest hand-washing station of <4.75 m had the lowest risk of IRH, followed by those with a mean distance of >6 m and then by those with a mean distance of 4.75 m to 6 m, as shown in Figure 5. Patients with an unknown mean distance of dialysis station to the nearest hand-washing station had an IRH risk that was somewhat similar to patients with a mean distance of >6 m. A log-rank test was done to determine if the curves were different from each other, resulting in a p-value of < 0.0001.

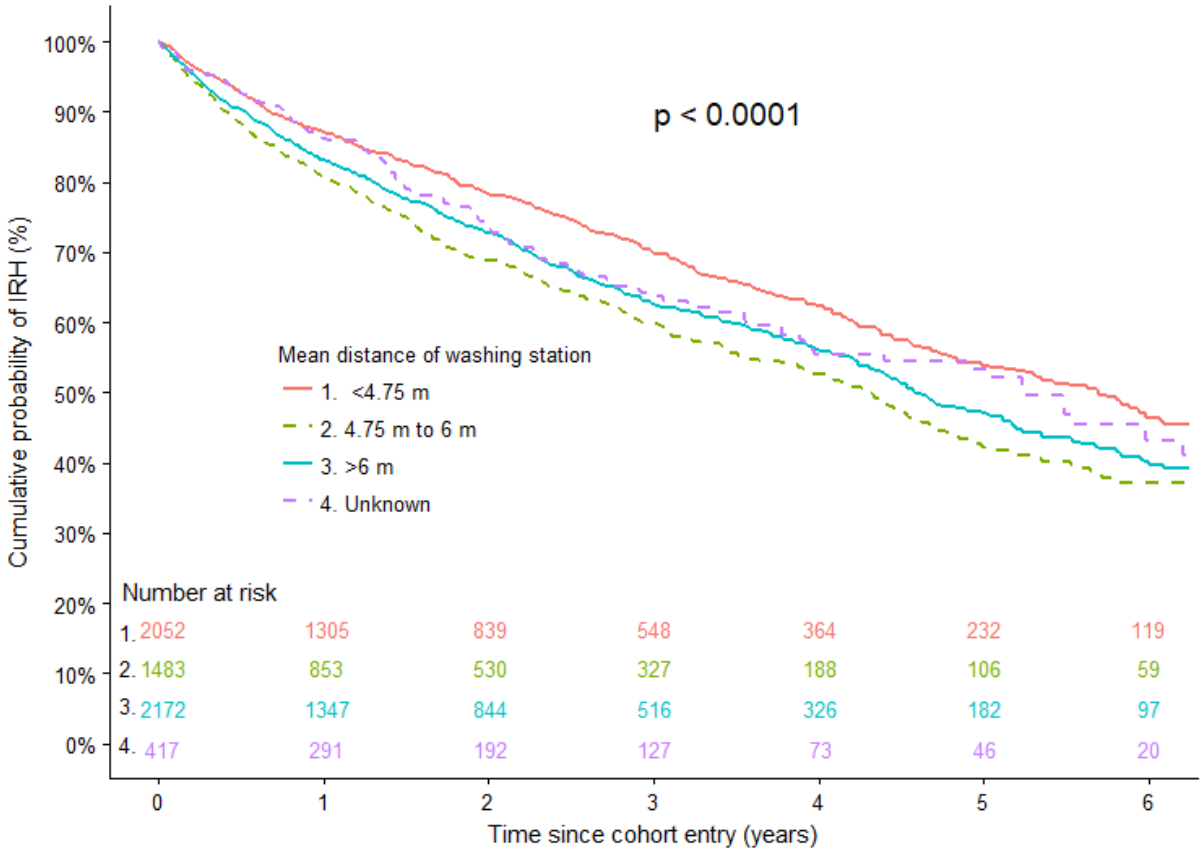

Figure 5. Unadjusted IRH-free Kaplan-Meier curves stratified by mean distance of dialysis station to hand-washing station (IRH, infection-related hospitalization)

Patients in dialysis facilities with a hand-washing station ratio of 3.15 to 3.75 had the lowest risk of IRH, followed by those with a hand-washing station ratio of over 3.75 and less than 3.15, as shown in Figure 6. The Kaplan-Meier curves for these two groups appears to be very similar. Patients with an unknown hand-washing station ratio seem to have an IRH risk somewhere in between. As before, the log rank test resulted in a p-value of < 0.0001, indicating that the curves are significantly different from each other.

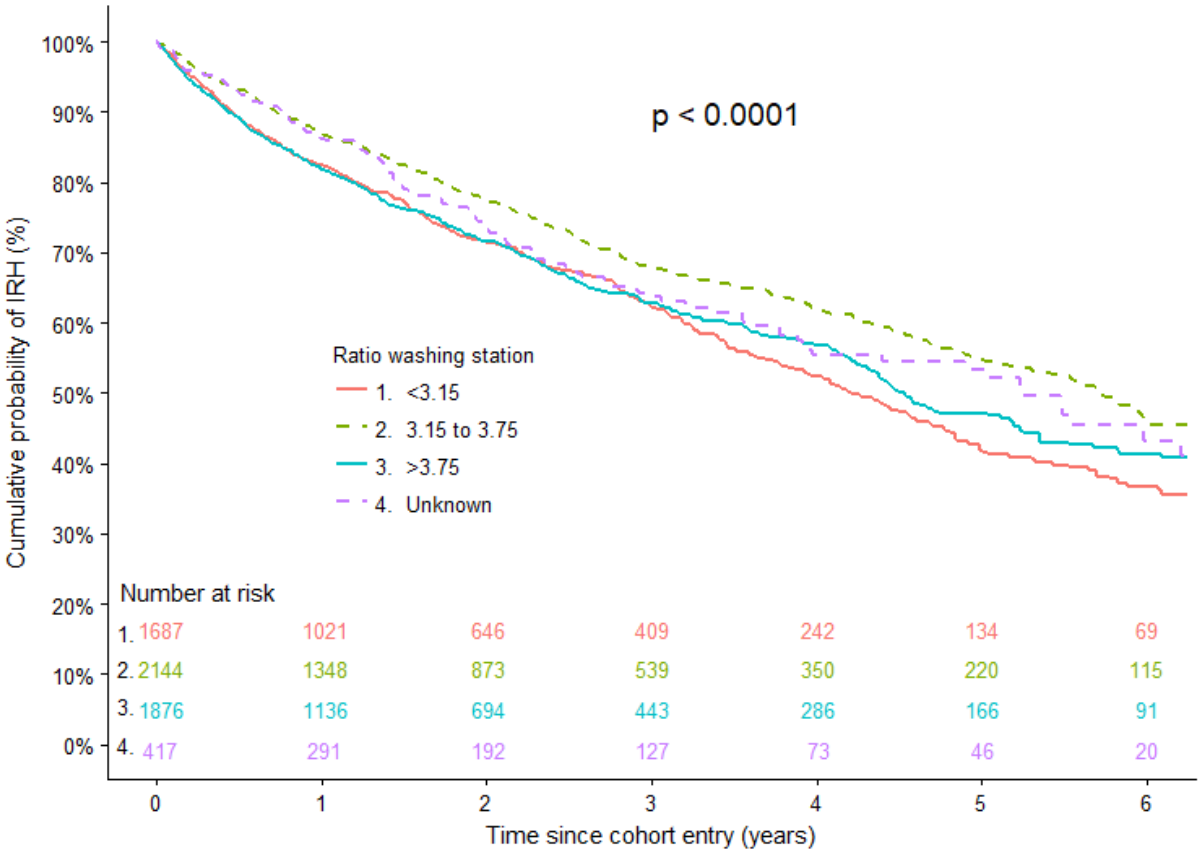

Figure 6. Unadjusted IRH-free Kaplan-Meier curves stratified by hand-washing station ratio (IRH, infection-related hospitalization)

Patients in dialysis facilities with a mean distance of dialysis station to ABHRD of 1.5 m to 3 m had the lowest risk of developing an IRH, followed by those with a mean distance of dialysis station to ABHRD of >3 m and those with a mean distance of <1.5 m. The risk of developing IRH seems to be similar for patients with a mean distance of dialysis station to ABHRD of >3 m or <1.5 m. As before, a log rank was done to test if the Kaplan-Meier curves were significantly different from each other, resulting in a p-value of 0.002.

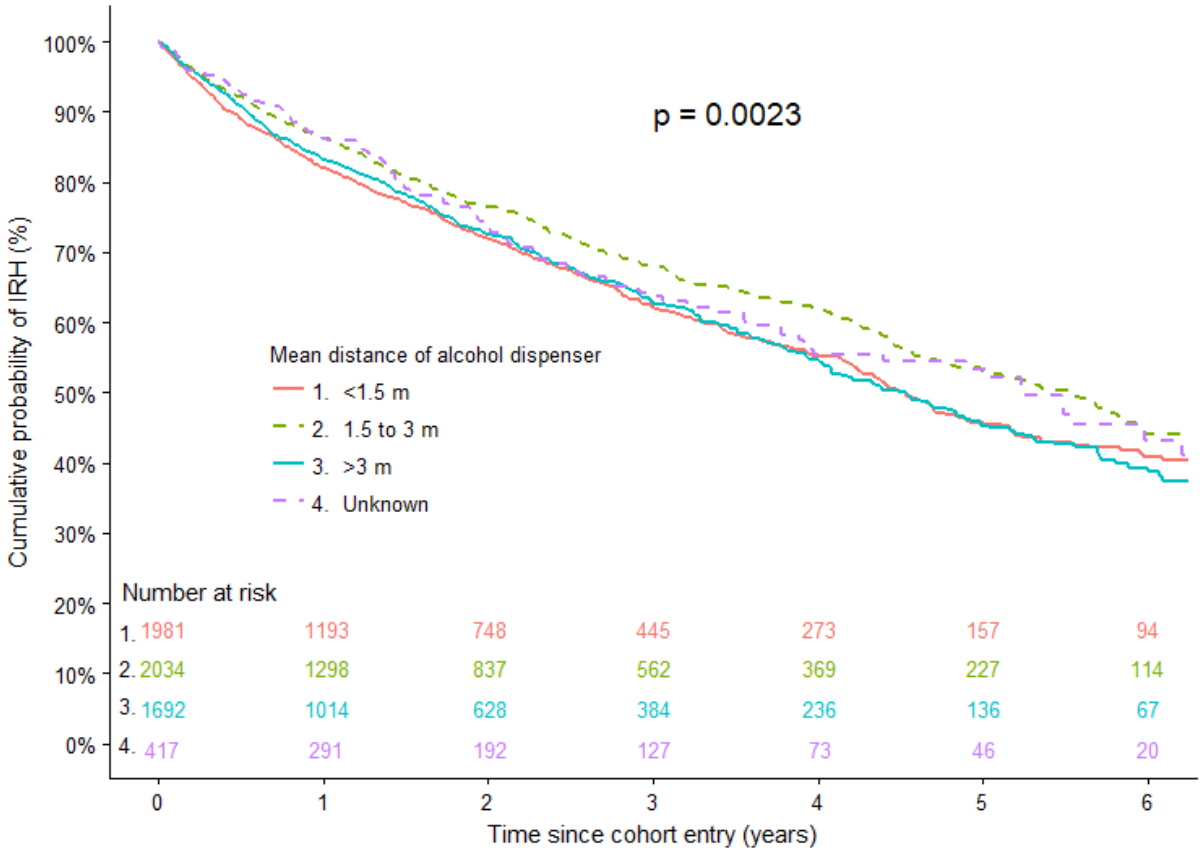

Figure 7. Unadjusted IRH-free Kaplan-Meier curves stratified by mean distance of dialysis station to ABHRD (IRH, infection-related hospitalization)

Patients with an ABHRD ratio of ≥1.5 had the lowest risk of developing an IRH, followed by those with an ABHRD ratio of <0.8 or 0.8 to <1.5. The risk of developing an IRH appears to be similar for patients in these two groups, as their Kaplan-Meier curves are almost identical. Patients with an unknown ABHRD ratio seem to be somewhere in the middle in terms of IRH risk. A log-rank test was performed, resulting in a p-value of <0.0001, indicating that the curves are significantly different from each other.

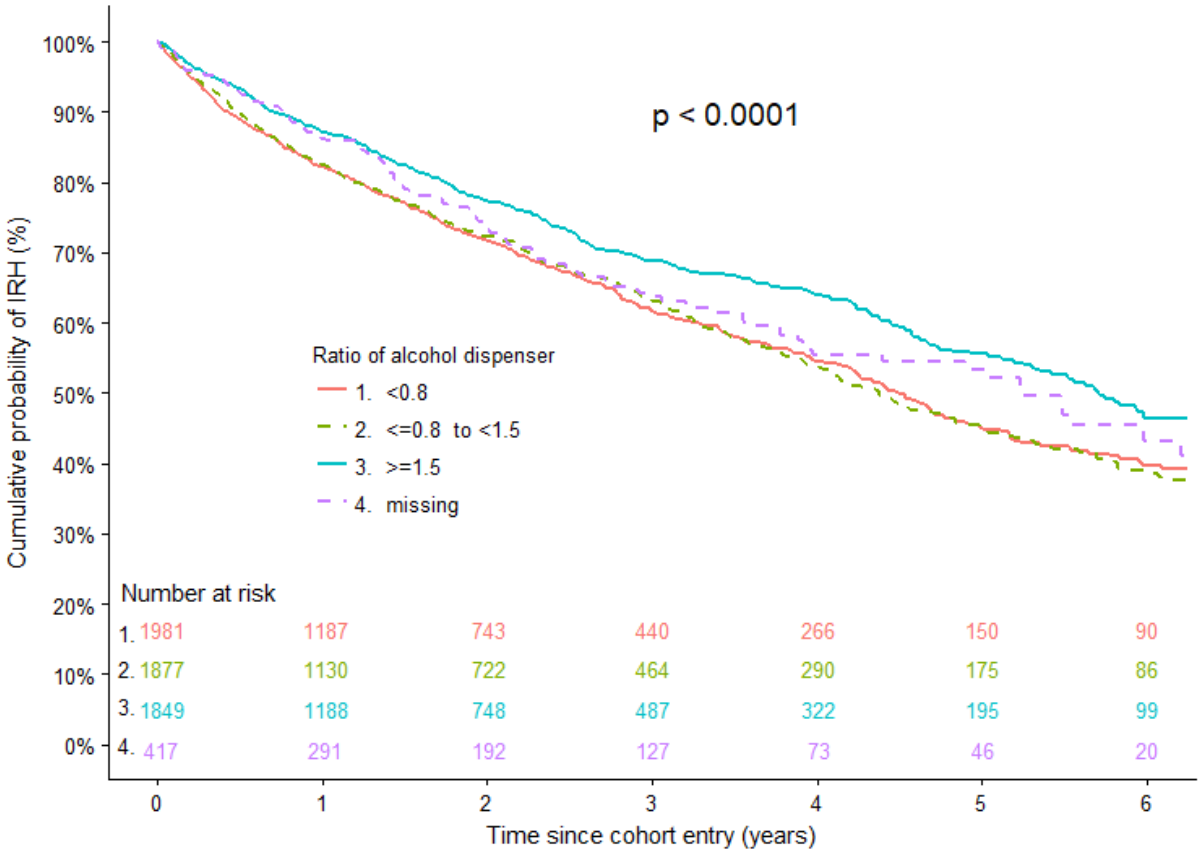

Figure 8. Unadjusted IRH-free Kaplan-Meier curves stratified by ABHRD ratio (IRH, infection-related hospitalization)

Sensitivity Analysis

Multiple sensitivity analyses were done to test the robustness of our results, as shown in Table 12. The first sensitivity analysis was done with the largest facility excluded. The second sensitivity analysis excluded prevalent patients. The third sensitivity analysis excluded patients with follow-up in two or more facilities (i.e. the patients who switched dialysis facility at least once during the course of their follow-up.) The fourth sensitivity analysis included steroids in the mixed effects Cox model, excluding all patients without RAMQ's drug insurance plan (and thus, anyone with a missing value for steroids).

The results for the sensibility analyses for mean distance of dialysis station to hand-washing station were somewhat similar to those of the main analysis. However, if the largest facility or prevalent patients were excluded, the association between IRH and a mean distance of 4.75 m to 6 m was no longer statistically significant.

For hand-washing station ratio, the results were very similar to those in the main analysis if prevalent patients were excluded. However, the association between IRH and a hand-washing station ratio of <3.15 was no longer statistically significant if the largest facility or patients with follow-up in 2 or more facilities were excluded.

The results of the sensitivity analyses for mean distance of dialysis station to ABHRD were very similar to the main analysis, and the interpretations remained the same.

However, there were some differences between the results of the main analysis and the sensitivity analysis for ABHRD ratio. An ABHRD ratio of ≥1.5 was no longer associated with a reduced risk of IRH if the largest facility was excluded or if patients with follow-up in 2 or more facilities were excluded.

The results of the sensitivity analysis for steroid use were very similar to the those of the main analysis for all of the facility-level variables. In all cases, the interpretation of the results remains the same regardless if steroids are added to the model.

It should be noted that there is no HR for patients with 'unknown' facility-level variables in the third sensitivity analysis simply because there were no patients in that category. Patients were only included in this study if they have a period of follow-up in a participating dialysis facility. However, in order to end up in the 'unknown' category, they must switch facilities

before suffering from their first IRH, which would automatically exclude them from the third sensitivity analysis.

Parameter	Adjusted Mixed Effects Cox Model				
	Main Analysis: Model without Steroids (n=6124)	**Largest facility excluded**	**Prevalent patients excluded**	**Patients with follow-up in 2 or more facilities excluded**	**Model with Steroids (n= 4793)**
	HR (95%CI)				
Mean distance of washing station					
Less than 4.75m (<4.75m)			Reference		
4.75 to 6m	1.30 (1.03, 1.64)	1.14 (1.00, 1.31)	1.32 (0.98, 1.77)	1.61 (1.22, 2.12)	1.32 (1.03, 1.69)
More than 6m (>6m)	1.13 (0.92, 1.40)	1.03 (0.91, 1.16)	1.04 (0.80, 1.36)	1.2 (0.95, 1.54)	1.18 (0.94, 1.48)
Unknown	1.13 (0.82, 1.58)	0.99 (0.81, 1.20)	1.18 (0.79, 1.76)		1.14 (0.79, 1.63)
Hand-washing station ratio					
Less than 3.15 (<3.15)	1.38 (1.08, 1.76)	1.10 (0.95, 1.26)	1.48 (1.08, 2.02)	1.28 (0.94 1.75)	1.36 (1.06, 1.75)
3.15 to 3.75			Reference		
More than 3.75 (>3.75)	1.19 (0.93, 1.51)	1.01 (0.88, 1.15)	1.34 (0.99, 1.83)	1.13 (0.83, 1.53)	1.18 (0.92, 1.51)
Unknown	1.20 (0.84, 1.72)	0.97 (0.79, 1.20)	1.39 (0.89, 2.16)		1.17 (0.80, 1.71)
Mean distance of dialysis station to ABHRD					
Less than 1.5m (<1.5m)	1.14 (0.88, 1.48)	1.01 (0.89, 1.14)	1.12 (0.82, 1.53)	1.17 (0.84 1.63)	1.16 (0.89, 1.52)
1.5m to 3m			Reference		
More than 3m (>3m)	1.13 (0.89, 1.43)	0.97 (0.85, 1.10)	1.11 (0.83, 1.48)	1.02 (0.75, 1.38)	1.14 (0.90, 1.46)
Unknown	1.10 (0.77, 1.57)	0.93 (0.77, 1.13)	1.17 (0.76, 1.78)		1.09 (0.74, 1.60)
ABHRD ratio					
Less than 0.8 (<0.8)	1.02 (0.81, 1.28)	1.03 (0.92, 1.15)	0.92 (0.68, 1.24)	1.15 (0.86, 1.54)	1.07 (0.85, 1.35)
0.8 to <1.5			Reference		
1.5 or more (≥1.5)	0.76 (0.60, 0.95)	0.94 (0.82, 1.07)	0.70 (0.52, 0.94)	0.85 (0.63, 1.13)	0.77 (0.61, 0.97)
Unknown	0.95 (0.68, 1.32)	0.93 (0.77, 1.13)	0.97 (0.64, 1.47)		0.94 (0.66, 1.34)

HR, hazard ratio; CI, confidence interval; ABHRD, alcohol-based hand rub dispenser

Table 12. Sensitivity Analysis: Mixed effects Cox model for first IRH

If a Kaplan Meier is done while excluding patients from largest facility, the Kaplan Meier curves become more similar to each other, as shown in Figures 9 to 12. For mean distance of dialysis station to hand-washing station (shown in Figure 9), the associations remained relatively similar compared to the those shown in Figure 5 in the main analysis, but they were much less pronounced. A log rank test was done, resulting in a p-value of 0.041, indicating that the curves were significantly different from each other.

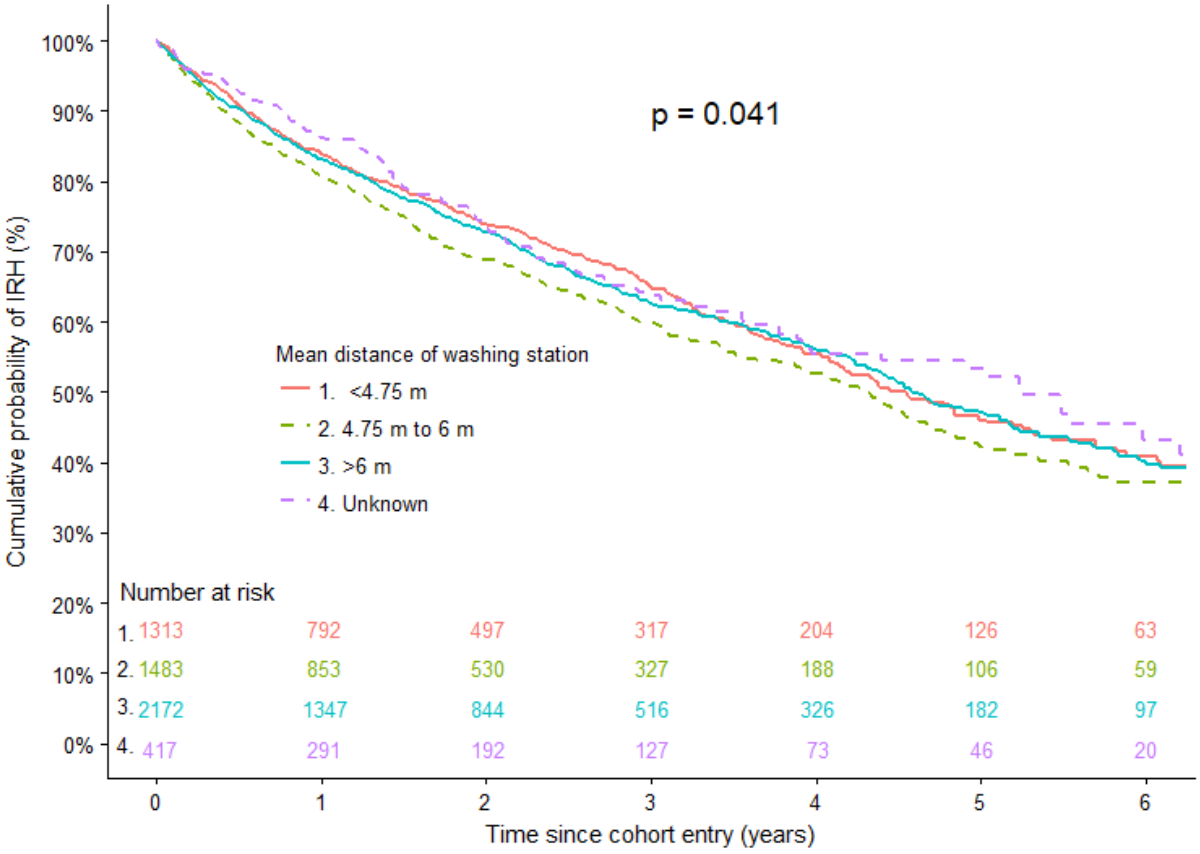

Figure 9. Sensitivity Analysis: Unadjusted IRH-free Kaplan-Meier curves stratified by mean distance of dialysis station to hand-washing station (IRH, infection-related hospitalization)

For the other three facility-level variables (hand-washing station ratio, mean distance of dialysis station to ABHRD and ABHRD ratio), the results changed dramatically once the largest facility was excluded from the cohort (shown in Figures 10 to 12). In the main analysis, the Kaplan-Meier curves were significantly different from each other, but in the sensitivity analyses, the Kaplan-Meier curves were no longer significantly different from each other. This implies that the largest facility may have been pulling on our results, and if it is excluded, there is no association between these facility-level variables and risk of suffering an IRH.

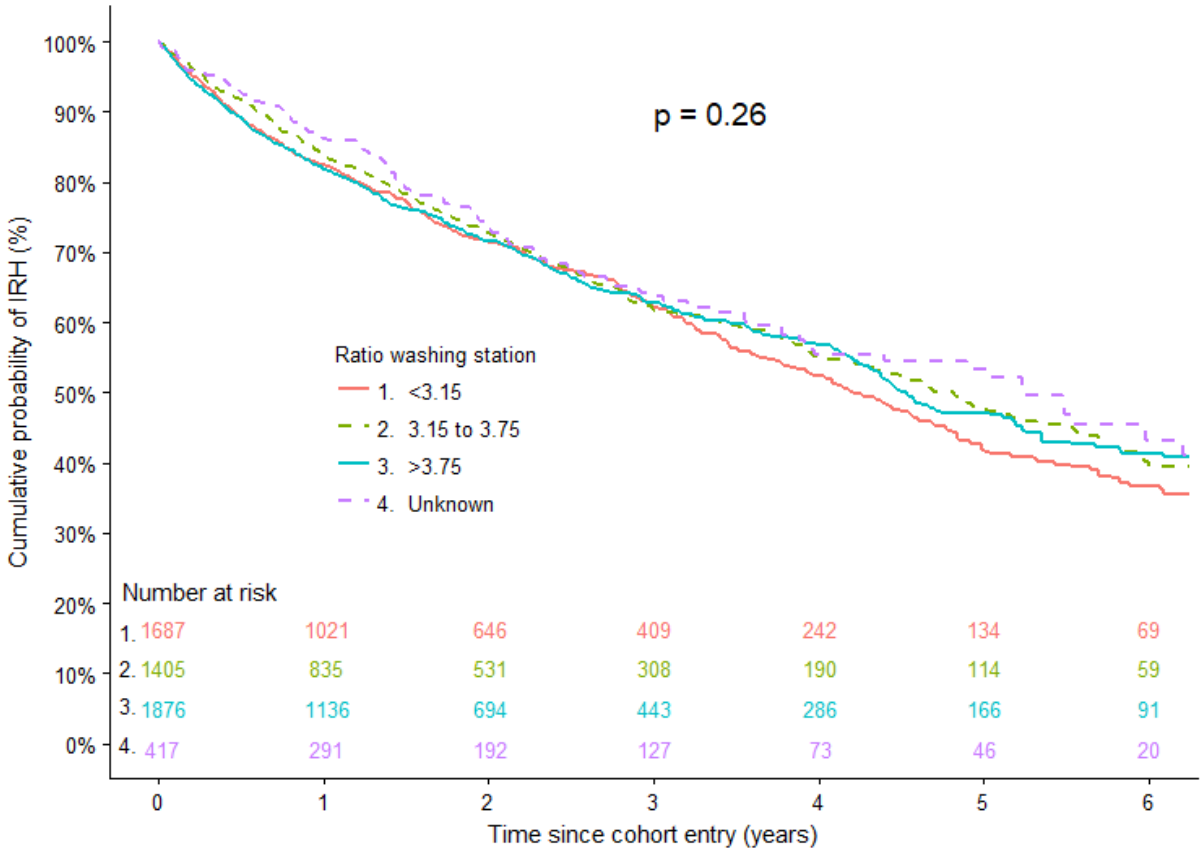

Figure 10. Sensitivity Analysis: Unadjusted IRH-free Kaplan-Meier curves stratified by hand-washing station ratio (IRH, infection-related hospitalization)

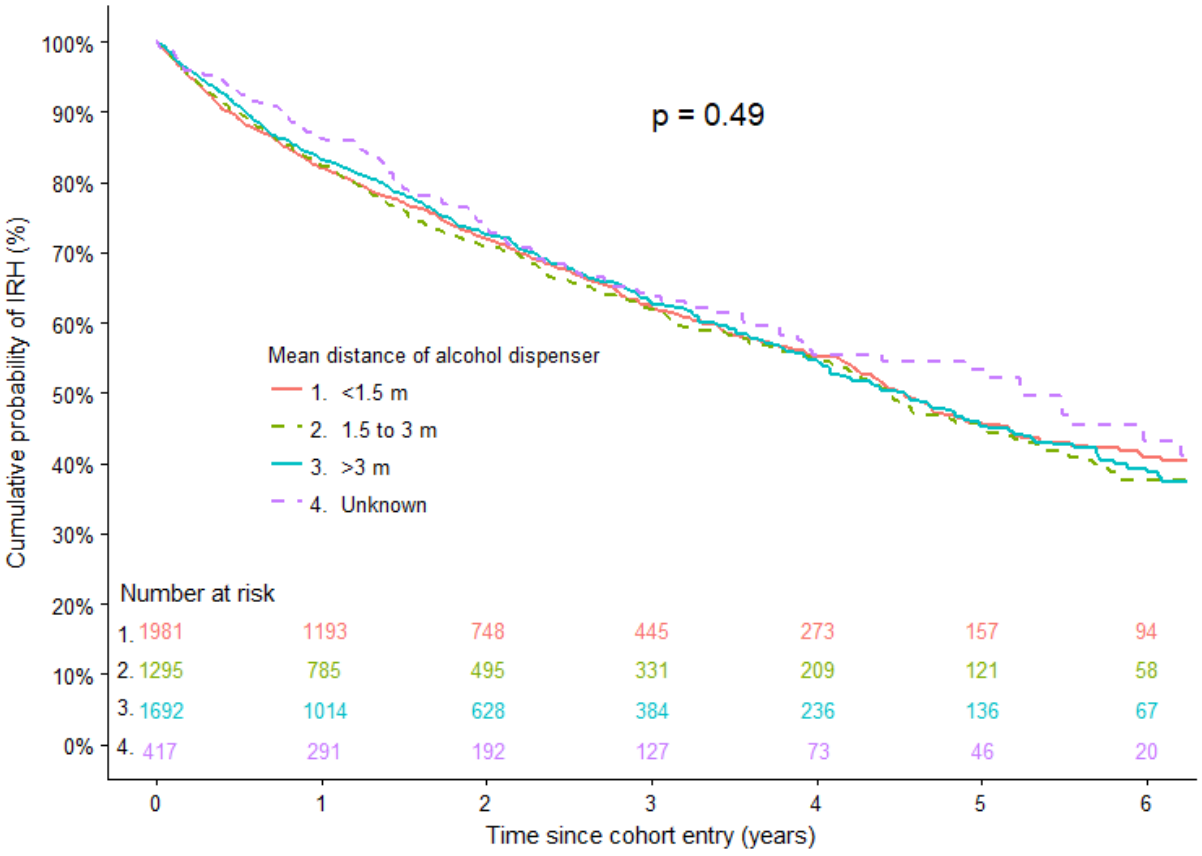

Figure 11. Sensitivity Analysis: Unadjusted IRH-free Kaplan-Meier curves stratified by mean distance of dialysis station to ABHRD (IRH, infection-related hospitalization)

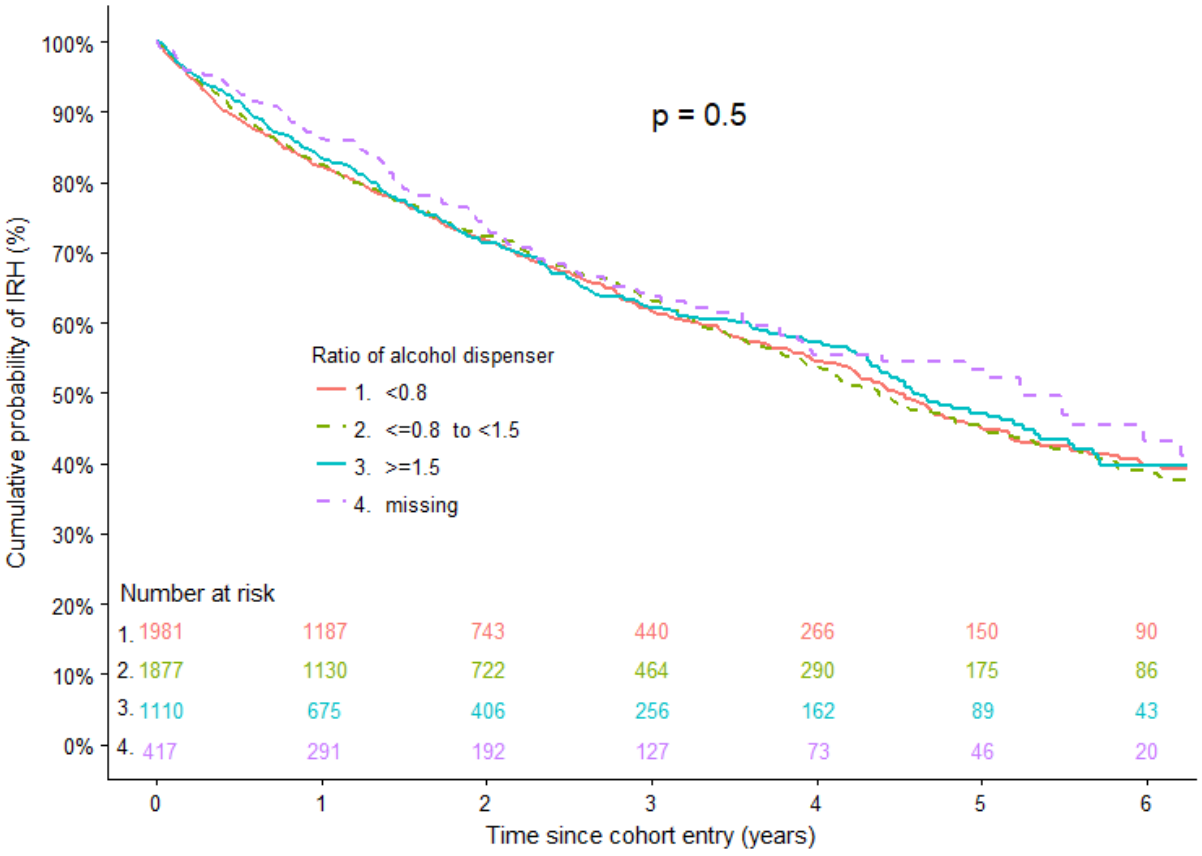

Figure 12. Sensitivity Analysis: Unadjusted IRH-free Kaplan-Meier curves stratified by ABHRD ratio (IRH, infection-related hospitalization)

Discussion

Summary of Results

Our results show that the association between mean distance of dialysis station to hand-washing station/ABHRD and hand-washing/ABHRD ratio to IRH is complex. There may be a non-monotonic association between IRH and these facility-level variables, but their association is unclear.

The overall IRH incidence across all participating facilities was 0.193 IRH per patient year (95%CI: 0.187, 0.200). There was a substantial variation in IRH rates between facilities in this study. However, this variation in IRH depending on the facility cannot be explained by the mean distance of dialysis station to hand-washing station/ABHRD and hand-washing/ABHRD ratio. There is likely something else that influences the IRH rates across different facilities.

A mean distance of dialysis station to hand-washing station of 4.75 m to 6 m was significantly associated with an increased risk of IRH, but there was no association between a mean distance of dialysis station to hand-washing station of >6 m and IRH. Likewise, a hand-washing station ratio of <3.15 was significantly associated with an increased risk of IRH, but a ratio of >3.75 was not significantly associated with an increased or decreased risk of IRH. Depending on what patients are excluded in the sensitivity analyses, these associations may disappear entirely.

There was no association between mean distance of dialysis station to the nearest ABHRD and IRH. Patients with an ABHRD ratio of ≥1.5 had a significantly lower risk of IRH. However, the association between ABHRD ratio and IRH did disappear depending on what sensitivity analysis was done.

Interpretation

There is little literature that examines the association between sink location or bed to sink ratio and hand-washing compliance. There are no studies we are aware of that directly examine the association of sink location or bed to sink ratio to infection rates, although it is known that increasing hand-washing compliance reduces infection transmission.[266-268]

Cloutman-Green et al.[279] found that sinks in more visible locations were used more frequently by staff in 3 pediatric intensive care units. Zellmer et al.[276] had similar results: placement of 2 additional sinks in highly visible locations increased hand-washing compliance in a surgical transplant unit. Deyneko et al.[277] found that hand-washing compliance was reduced when the sink was too far away, when health-care workers had to make 2 or more 90° turns to reach the sink and if the sink was not in direct line of sight from the patient room. Kaplan et al.[278] compared two ICUs, one with a bed to sink ratio of 4:1 and another with a bed to sink ratio of 1:1. Nurses in the ICU with a bed to sink ratio of 1:1 had a significantly greater number of hand-washes compared to those in the ICU with a bed to sink ratio of 4:1.

In our study, there was no way to measure visibility or convenience objectively. Thus, distance from dialysis station to the nearest hand-washing station was used as a proxy for visibility and convenience. Hand-washing station ratio in our study also corresponds to bed to sink ratio in these studies.

Our results do not support theirs, although it is unclear if this is due to differences in study setting or population or possibly due to the weaker link between hand-washing compliance and hand-washing station number or location in the hemodialysis population.

Notably, Whitby et al.[280] examined the association between hand-washing compliance and sink accessibility in a rebuilt and relocated tertiary hospital. The new hospital design ensured that staff were no more than 5 m away from a sink for their clinical duties. Unlike the previous studies, Whitby et al. observed multiple wards, not just the ICU, and found that improved sink accessibility did not improve hand-washing compliance.

There are also articles devoted to the association between dispenser location or bed to dispenser ratio and hand-washing compliance. For most part, the results are similar to those found with sink location or bed to sink ratio in that increasing dispenser availability or putting dispensers in convenient locations usually increases hand-washing compliance.

Various studies have tested how the availability of ABHRD impacts hand-washing compliance. Bischoff et al.[281] found that compliance increased when there was a bed to dispenser ratio of 1:1 compared with a bed to dispenser ratio of 4:1. Haas et al.[282] tested whether availability of a personal wearable alcohol hand sanitizer dispenser increased

compliance. While the intervention did initially increase compliance, the improvement was not sustained long-term. Likewise, Giannitsioti et al.[283] performed a similar study, this time testing if a bed rail system of ABHR antiseptics increased compliance. Their results were similar to those of Haas et al. They observed that there was an increase in compliance during the first intervention period but the improvement was not sustained. These studies show that while increased availability of ABHRDs may increase compliance in the short term, they may not be associated with increased compliance in the long term.

ABHRD location has been linked to compliance in other studies. Birnbach et al.[274] found that compliance increased when dispensers were placed in a more convenient location (i.e. in clear view of the physician). Likewise, Boog et al.[284] and Thomas et al.[275] found that compliance increased when dispensers were placed in 'conspicuous locations.' In the case of the latter study, the dispensers in 'conspicuous locations' were placed immediately proximate to the patients' beds. In the case of the former study, Boog et al. studied which locations were associated with the highest compliance based on feedback of healthcare workers. In general, healthcare workers preferred dispensers that were within their line of sight, on the workflow route, near the sink, patient or computer, not in a route obstructed by people or objects or in a familiar location.

As with the hand-washing station analysis, mean distance of dialysis station to nearest ABHRD and ABHRD ratio were used as proxies for convenience and availability respectively. However, our study analyzed IRH risk, not hand-washing compliance. While there is a well-known link between hand-washing compliance and infection transmission in the general healthcare setting,[266-269] it is unclear how the two are linked in the hemodialysis patient population. It is possible that there is a link, given that hemodialysis patients are particularly prone to infection, as they have impaired immune systems and are reliant on vascular access for hemodialysis.

However, our results show that there is a non-monotonic association between IRH rates and mean distance of dialysis station to the nearest hand-washing station/ABHRD and hand-washing station/ABHRD ratio. Depending on the sensitivity analysis done, there may be no association between them at all. It is also likely that there may be other factors (or a combination of factors) that influence the IRH rates in the dialysis population besides these

facility level variables. Elucidating the exact association between hand hygiene compliance, ABHRD and hand-washing availability and location and IRH rates would require more detailed studies.

Strengths and Weaknesses of this study

The strengths of our study include its large sample size and high statistical power. It includes 21 dialysis facilities across Quebec and linked data from RAMQ and Med-Echo. Most dialysis facilities in Quebec have agreed to participate in this study and many patients rely on RAMQ as their source of healthcare insurance, thus allowing us to include most dialysis patients in Quebec.

Also, our study includes a combination of existing data and new variables measured at each participating dialysis facility not included in most databases. In this case, these variables are the mean distance of the hand-washing station or ABHRD to the nearest dialysis station and hand-washing station/ABHRD ratio.

However, our study also has considerable limitations, mostly due to its nature as an observational study. This means that we can only find associations between different variables, not causality, as well as the presence of selection bias, information bias and confounding variables that remain unaccounted for despite our best efforts.

IRH rates vary considerably across different facility. Despite including most dialysis patients in Quebec, not including all facilities in Quebec (especially the larger facilities) may have affected our results.

One source of information bias is the fact that we analyzed the mean distance of dialysis station to the nearest hand-washing station/ABHRD. The larger dialysis facilities have multiple rooms devoted to hemodialysis sessions and thus, the mean distance of dialysis station to the nearest hand-washing station/ABHRD could vary even within the same dialysis facility depending on the room.

Our measurements for the hand-washing station and ABHRD-related variables were also quite homogenous, with ABHRD variables being the most homogenous. For example, the ABHRD ratio varied between about 0.6 to 3 and the mean distance of dialysis station to nearest ABHRD varied between 0.9 m to 4.6 m. As a result, it is hard to tell if the availability and placement of hand-washing stations and ABHRDs truly affect the incidence of IRH in the

context of this study. It is possible that a significantly increased incidence of IRH will only appear at much higher values.

Another limitation is that we were unfortunately unable to access data from the Canadian Organ Replacement Register (CORR). CORR is a national information system for organ replacement therapies whose mandate is to record, analyze and report on vital organ transplantation and renal dialysis in Canada. It is notable for offering data that is normally not available in provincial administrative databases, such as the patient's type of vascular access and their laboratory results (such as serum albumin, hemoglobin, creatinine, among others). As a result, we could not adjust for these possible risk factors due to the lack of data. Their association with infection has been examined in many studies.

For example, many studies have shown that a patient's vascular access has a considerable impact on their risk of suffering an infection, with patients using a CVC being the most vulnerable.[23-27] While the vast majority of studies agree that a patient's risk of infection is impacted by the type of vascular access they use, results concerning laboratory results are less clear.

For example, one study showed that higher phosphorous levels were associated with increased risk of IRH, but the same was not true for albumin, eGFR, urea or hemoglobin.[242] In contrast, other studies have suggested that a low albumin increased the risk of septicemia among dialysis patients [209], was associated with higher infection severity[208, 255] and was associated with a higher risk of infection-related events (in older patients).[256]

Lower eGFR (used to measure kidney function) have been associated with a higher risk of IRH [257] and bloodstream infections in older patients with CKD.[258] Two other studies found that lower serum creatinine, albumin or BMI are associated with higher mortality.[259, 260] Hemoglobin's association with infection is unclear. On one hand, lower hemoglobin has been associated with increased risk of bacteremia[261] and vascular access infection.[262] On the other hand, other studies have found a non-monotonic[256] or non-existent[263] association between hemoglobin and infection in hemodialysis patients.

Also, information relating to S. aureus nasal carriers and what vaccinations, topical antibiotics or antibiotic locks were administered to participating hemodialysis patients was not available in either the RAMQ or Med-Echo databases used in this study. While the literature does indicate that there is an association between poor hand hygiene and access-related

infection,[187, 285-287] we do not have the data to study this association. As a result, we could not adjust for these variables in our analyses.

It should be noted that we use various administrative codes in our analysis, rather than patient files. These codes within the RAMQ and Med-Echo databases were used to determine the patients' dialysis modality (and whether they were chronic hemodialysis patients), if they suffered an IRH (and what type) and their comorbidities. Only codes that have been written down and imputed into these databases are known to us, and thus the sensitivity and the specificity of data is not perfect. There are also other limitations. These codes do not mention the severity of the disease and infections that do not require hospitalization. As a result, some residual confounders may be present in our study.

Also, in the case of prevalent patients, we cannot tell if their comorbidities are risk factors or a consequence of hemodialysis. Some comorbidities can even be both causes and consequences of ESRD, such as hypertension.

Conclusion

The goal of this study was to elucidate the association between distance of dialysis station to nearest hand-washing station/ABHRD and hand-washing station/ABHRD ratio and IRH rates in the chronic hemodialysis patient population. Our analysis was based on data collected at various participating hemodialysis units and linked data from RAMQ and Med-Echo. It allows us to conclude that the association between these facility-level variables and IRH rates is unclear, especially as our results seem to be change after certain sensitivity analyses are done. It is likely that there is something else that influences IRH rates besides the facility-level variables studied. More studies would be required to determine what factors are responsible for the varying IRH rates across different facilities.

Conclusion

Our study aimed to elucidate the association between various facility-level variables (patient to nurse ratio, distance of dialysis station to nearest hand-washing station/ABHRD and hand-washing station/ABHRD ratio) and risk of IRH in the hemodialysis patient population. Linked data from the RAMQ and Med-Echo allowed us to adjust for multiple confounding variables, although there may still be some residual confounders due to the limitations of these databases.

However, our results in all cases were non-monotonic and did not depict a clear association between these facility-level variables and risk of IRH. If the largest facility was excluded from the cohort, these non-monotonic associations disappeared entirely.

This was most likely because some facilities in our studies had facility-level variables that would be considered 'disadvantageous' in terms of preventing IRH (for example, high patient to nurse ratio, high hand-washing station/ABHRD ratio, etc.) and yet had low IRH rates. It indicates that that there is something else that influences IRH rates across facilities besides the facility-level variables analyzed in this study.

It is also possible that there could be an interaction between hand hygiene adherence, distance between sinks/ABHRDs and patient to nurse ratio. However, we were unable to directly study hand hygiene adherence due to lack of data. Hand hygiene adherence was not evaluated during our visits to participating facilities, and the RAMQ and Med-Echo did not have data relating to hand hygiene adherence.

Thus, elucidating the relationship between hand hygiene adherence, distance between sinks/ABHRDs and patient to nurse ratio would require additional studies. More studies would also be needed to determine the relationship between facility-level variables and IRH rates.

Bibliography

1. Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL. *Brenner & Rector's The Kidney.* Tenth Edition ed. United States: Philadelphia, PA : Elsevier; 2016.

2. Seifert ME, Hruska KA. The Kidney-Vascular-Bone Axis in the Chronic Kidney Disease-Mineral Bone Disorder. *Transplantation.* 2016;100:497-505.

3. Hruska KA, Seifert M, Sugatani T. Pathophysiology of the Chronic Kidney Disease – Mineral Bone Disorder (CKD-MBD). *Curr. Opin. Nephrol. Hypertens.* 2015;24:303-309.

4. Bover J, Cozzolino M. Mineral and bone disorders in chronic kidney disease and end-stage renal disease patients: new insights into vitamin D receptor activation. *Kidney International Supplements.* 2011;1:122-129.

5. Campean V, Neureiter D, Varga I, et al. Atherosclerosis and vascular calcification in chronic renal failure. *Kidney Blood Press. Res.* 2005;28:280-289.

6. Tsimihodimos V, Mitrogianni Z, Elisaf M. Dyslipidemia Associated with Chronic Kidney Disease. *The Open Cardiovascular Medicine Journal.* 2011;5:41-48.

7. Mikolasevic I, Žutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. *Int. J. Nephrol. Renovasc. Dis.* 2017;10:35-45.

8. United States Renal Data System. 2016 Annual Data Report: epidemiology of kidney disease in the United States: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 2016.

9. Canadian Institute for Health Information. Annual Statistics on Organ Replacement in Canada - Dialysis, Transplantation and Donation, 2007 to 2016. In: CIHI, ed. Ottawa2017.

10. Arora P, Vasa P, Brenner D, et al. Prevalence estimates of chronic kidney disease in Canada: results of a nationally representative survey. *CMAJ.* 2013;185:E417-423.

11. National Institute of Diabetes & Digestive & Kidney Diseases. Choosing a Treatment for Kidney Failure. Vol 2017. United States.

12. Fishbane S, Mathew A, Vaziri ND. Iron toxicity: relevance for dialysis patients. *Nephrol. Dial. Transplant.* 2014;29:255-259.

13. Ishida JH, Johansen KL. Iron and infection in hemodialysis patients. *Seminars in dialysis.* 2014;27:26-36.

14. Jadeja YP, Kher V. Protein energy wasting in chronic kidney disease: An update with focus on nutritional interventions to improve outcomes. *Indian J. Endocrinol. Metab.* 2012;16:246-251.

15. National Institute of Diabetes & Digestive & Kidney Diseases. Hemodialysis. Vol 2017. United States.

16. Hossny A. Brachiobasilic arteriovenous fistula: Different surgical techniques and their effects on fistula patency and dialysis-related complications. *J. Vasc. Surg.* 2003;37:821-826.

17. Santoro D, Benedetto F, Mondello P, et al. Vascular access for hemodialysis: current perspectives. *Int. J. Nephrol. Renovasc. Dis.* 2014;7:281-294.

18. Lok CE. Fistula first initiative: advantages and pitfalls. *Clin. J. Am. Soc. Nephrol.* 2007;2:1043-1053.

19. USC Vascular Surgery. Vascular Access. Vol 2017. Los Angeles, CA.

20. Surgery V. Vascular Access University of Southern California Department of Surgery.

21. Feldman HI, Kobrin S, Wasserstein A. Hemodialysis vascular access morbidity. *J. Am. Soc. Nephrol.* 1996;7:523-535.

22. National Institute of Diabetes & Digestive & Kidney Diseases. Vascular Access for Hemodialysis. Vol 2017. United States.

23. Bray BD, Boyd J, Daly C, et al. Vascular access type and risk of mortality in a national prospective cohort of haemodialysis patients. *QJM: An International Journal of Medicine.* 2012;105:1097-1103.

24. Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. *Kidney Int.* 2001;60:1443-1451.

25. Allon M, Depner TA, Radeva M, et al. Impact of dialysis dose and membrane on infection-related hospitalization and death: results of the HEMO Study. *J. Am. Soc. Nephrol.* 2003;14:1863-1870.

26. Pastan S, Soucie JM, McClellan WM. Vascular access and increased risk of death among hemodialysis patients. *Kidney Int.* 2002;62:620-626.

27. Lafrance JP, Rahme E, Lelorier J, Iqbal S. Vascular access-related infections: definitions, incidence rates, and risk factors. *Am. J. Kidney Dis.* 2008;52:982-993.

28. Rayner HC, Besarab A, Brown WW, Disney A, Saito A, Pisoni RL. Vascular access results from the Dialysis Outcomes and Practice Patterns Study (DOPPS): performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. *Am. J. Kidney Dis.* 2004;44:22-26.

29. Almasri J, Alsawas M, Mainou M, et al. Outcomes of vascular access for hemodialysis: A systematic review and meta-analysis. *J. Vasc. Surg.* 2016;64:236-243.

30. System USRD. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. : National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 2016.

31. Cdspdin-h (SPIN-HD). Vascular Access–Related Bloodstream Infections in Hemodialysis Patients - Surveillance results: 2016-20172017.

32. Plotkin SA, Orenstein WA, Offit PA. Section 1: General aspects of vaccination. *Vaccines*. Scotland: Elsevier/Saunders; 2013.

33. Vaziri ND, Pahl MV, Crum A, Norris K. EFFECT OF UREMIA ON STRUCTURE AND FUNCTION OF IMMUNE SYSTEM. *Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation.* 2012;22:149-156.

34. Meyer TW, Hostetter TH. Approaches to uremia. *J. Am. Soc. Nephrol.* 2014;25:2151-2158.

35. Moradi H, Sica DA, Kalantar-Zadeh K. Cardiovascular Burden Associated with Uremic Toxins in Patients with Chronic Kidney Disease. *Am. J. Nephrol.* 2013;38:136-148.

36. Burn D, Bates D. Neurology and the kidney. *Journal of Neurology, Neurosurgery, and Psychiatry.* 1998;65:810-821.

37. Arnold R, Issar T, Krishnan AV, Pussell BA. Neurological complications in chronic kidney disease. *JRSM Cardiovascular Disease.* 2016;5:2048004016677687.

38. Carrero J, Aguilera A, Stenvinkel P, Gil F, Selgas R, Lindholm B. *Appetite Disorders in Uremia*2008.
39. London GM, Parfrey PS. Cardiac Disease in Chronic Uremia: Pathogenesis. *Adv. Ren. Replace. Ther.*;4:194-211.
40. Cohen G, Haag-Weber M, Horl WH. Immune dysfunction in uremia. *Kidney Int. Suppl.* 1997;62:S79-82.
41. Hauser AB, Stinghen AE, Kato S, et al. Characteristics and causes of immune dysfunction related to uremia and dialysis. *Perit. Dial. Int.* 2008;28 Suppl 3:S183-187.
42. Girndt M, Sester U, Sester M, Kaul H, Kohler H. Impaired cellular immune function in patients with end-stage renal failure. *Nephrol. Dial. Transplant.* 1999;14:2807-2810.
43. Kaysen GA. Inflammation: cause of vascular disease and malnutrition in dialysis patients. *Semin. Nephrol.* 2004;24:431-436.
44. Yoon JW, Pahl MV, Vaziri ND. Spontaneous leukocyte activation and oxygen-free radical generation in end-stage renal disease. *Kidney Int.* 2007;71:167-172.
45. Gollapudi P, Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Leukocyte toll-like receptor expression in end-stage kidney disease. *Am. J. Nephrol.* 2010;31:247-254.
46. Hendrikx TK, van Gurp EA, Mol WM, et al. End-stage renal failure and regulatory activities of CD4+CD25bright+FoxP3+ T-cells. *Nephrol. Dial. Transplant.* 2009;24:1969-1978.
47. Alexiewicz JM, Smogorzewski M, Fadda GZ, Massry SG. Impaired phagocytosis in dialysis patients: studies on mechanisms. *Am. J. Nephrol.* 1991;11:102-111.
48. Massry SG, Smogorzewski M. Dysfunction of polymorphonuclear leukocytes in uremia: Role of parathyroid hormone. *Kidney Int.* 2001;59:S195-S196.
49. Betjes MGH, Meijers RWJ, Litjens NHR. Loss of Renal Function Causes Premature Aging of the Immune System. *Blood Purif.* 2013;36:173-178.
50. Betjes MGH, Langerak AW, van der Spek A, de Wit EA, Litjens NHR. Premature aging of circulating T cells in patients with end-stage renal disease. *Kidney Int.* 2011;80:208-217.
51. Agrawal S, Gollapudi P, Elahimehr R, Pahl MV, Vaziri ND. Effects of end-stage renal disease and haemodialysis on dendritic cell subsets and basal and LPS-stimulated cytokine production. *Nephrol. Dial. Transplant.* 2010;25:737-746.
52. Hesselink DA, Betjes MG, Verkade MA, Athanassopoulos P, Baan CC, Weimar W. The effects of chronic kidney disease and renal replacement therapy on circulating dendritic cells. *Nephrol. Dial. Transplant.* 2005;20:1868-1873.
53. Verkade MA, van Druningen CJ, Vaessen LM, Hesselink DA, Weimar W, Betjes MG. Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. *Nephrol. Dial. Transplant.* 2007;22:128-138.
54. Meier P, Dayer E, Blanc E, Wauters JP. Early T cell activation correlates with expression of apoptosis markers in patients with end-stage renal disease. *J. Am. Soc. Nephrol.* 2002;13:204-212.
55. Matsumoto Y, Shinzato T, Amano I, et al. Relationship between susceptibility to apoptosis and Fas expression in peripheral blood T cells from uremic patients: a possible mechanism for lymphopenia in chronic renal failure. *Biochem. Biophys. Res. Commun.* 1995;215:98-105.
56. Moser B, Roth G, Brunner M, et al. Aberrant T cell activation and heightened apoptotic turnover in end-stage renal failure patients: a comparative evaluation

between non-dialysis, haemodialysis, and peritoneal dialysis. *Biochem. Biophys. Res. Commun.* 2003;308:581-585.

57. Yoon JW, Gollapudi S, Pahl MV, Vaziri ND. Naïve and central memory T-cell lymphopenia in end-stage renal disease. *Kidney Int.* 2006;70:371-376.

58. Fernandez-Fresnedo G, Ramos MA, Gonzalez-Pardo MC, de Francisco AL, Lopez-Hoyos M, Arias M. B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol. Dial. Transplant.* 2000;15:502-510.

59. Pahl MV, Gollapudi S, Sepassi L, Gollapudi P, Elahimehr R, Vaziri ND. Effect of end-stage renal disease on B-lymphocyte subpopulations, IL-7, BAFF and BAFF receptor expression. *Nephrology Dialysis Transplantation.* 2010;25:205-212.

60. Law MR, Watt HC, Wald NJ. The underlying risk of death after myocardial infarction in the absence of treatment. *Arch. Intern. Med.* 2002;162:2405-2410.

61. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations) In: Bethesda M, ed: National Cancer Institute; 2012.

62. Canadian Institute for Health Information. Treatment of End-Stage Organ Failure in Canada, 2004 to 2013 (2015 Annual Report). In: CIHI, ed. Ottawa2015.

63. U.S. Renal Data System. USRDS 2011 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 2011.

64. Marr KA, Sexton DJ, Conlon PJ, Corey GR, Schwab SJ, Kirkland KB. Catheter-related bacteremia and outcome of attempted catheter salvage in patients undergoing hemodialysis. *Ann. Intern. Med.* 1997;127:275-280.

65. Jean G, Charra B, Chazot C, et al. Risk factor analysis for long-term tunneled dialysis catheter-related bacteremias. *Nephron.* 2002;91:399-405.

66. Taylor G, Gravel D, Johnston L, Embil J, Holton D, Paton S. Incidence of bloodstream infection in multicenter inception cohorts of hemodialysis patients. *Am. J. Infect. Control.* 2004;32:155-160.

67. Davis C. Normal Flora. In: Baron S, ed. *Medical Microbiology*. 4th ed. Galveston (TX): University of Texas Medical Branch at Galveston; 1996.

68. Skov Dalgaard L, Norgaard M, Jespersen B, et al. Risk and Prognosis of Bloodstream Infections among Patients on Chronic Hemodialysis: A Population-Based Cohort Study. *PLoS One.* 2015;10:e0124547.

69. D'Amato-Palumbo S, Kaplan AA, Feinn RS, Lalla RV. Retrospective study of microorganisms associated with vascular access infections in hemodialysis patients. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology.* 2013;115:56-61.

70. Danese MD, Griffiths RI, Dylan M, Yu H-T, Dubois R, Nissenson AR. Mortality differences among organisms causing septicemia in hemodialysis patients. *Hemodialysis International.* 2006;10:56-62.

71. Suzuki M, Satoh N, Nakamura M, Horita S, Seki G, Moriya K. Bacteremia in hemodialysis patients. *World J Nephrol.* 2016;5:489-496.

72. Piraino B. Staphylococcus aureus infections in dialysis patients: focus on prevention. *ASAIO J.* 2000;46:S13-17.

73. Mokrzycki MH, Zhang M, Cohen H, Golestaneh L, Laut JM, Rosenberg SO. Tunnelled haemodialysis catheter bacteraemia: risk factors for bacteraemia recurrence,

infectious complications and mortality. *Nephrology Dialysis Transplantation.* 2006;21:1024-1031.

74. Sexton DJ. Vascular access infections in patients undergoing dialysis with special emphasis on the role and treatment of Staphylococcus aureus. *Infect. Dis. Clin. North Am.* 2001;15:731-742, vii.

75. Engemann JJ, Friedman JY, Reed SD, et al. Clinical outcomes and costs due to Staphylococcus aureus bacteremia among patients receiving long-term hemodialysis. *Infect. Control Hosp. Epidemiol.* 2005;26:534-539.

76. Fram D, Okuno MF, Taminato M, et al. Risk factors for bloodstream infection in patients at a Brazilian hemodialysis center: a case-control study. *BMC Infect. Dis.* 2015;15:158.

77. Vandecasteele SJ, Boelaert JR, De Vriese AS. Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. *Clin. J. Am. Soc. Nephrol.* 2009;4:1388-1400.

78. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the Prevention of Intravascular Catheter-related Infections. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America.* 2011;52:e162-e193.

79. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet.* 2000;356.

80. Pessoa-Silva CL, Hugonnet S, Pfister R, et al. Reduction of health care associated infection risk in neonates by successful hand hygiene promotion. *Pediatrics.* 2007;120:e382-390.

81. Lam BCC, Lee J, Lau YL. Hand Hygiene Practices in a Neonatal Intensive Care Unit: A Multimodal Intervention and Impact on Nosocomial Infection. *Pediatrics.* 2004;114:e565.

82. Johnson PD, Martin R, Burrell LJ, et al. Efficacy of an alcohol/chlorhexidine hand hygiene program in a hospital with high rates of nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection. *Med. J. Aust.* 2005;183:509-514.

83. Johnson DW, Fleming SJ. The use of vaccines in renal failure. *Clin. Pharmacokinet.* 1992;22:434-446.

84. Grzegorzewska AE. Hepatitis B Vaccination in Chronic Kidney Disease: Review of Evidence in Non-Dialyzed Patients. *Hepat. Mon.* 2012;12:e7359.

85. Janus N, Vacher L-V, Karie S, Ledneva E, Deray G. Vaccination and chronic kidney disease. *Nephrology Dialysis Transplantation.* 2008;23:800-807.

86. Rangel MC, Coronado VG, Euler GL, Strikas RA. Vaccine recommendations for patients on chronic dialysis. The Advisory Committee on Immunization Practices and the American Academy of Pediatrics. *Seminars in dialysis.* 2000;13:101-107.

87. Recommendations of the Advisory Committee on Immunization Practices (ACIP): use of vaccines and immune globulins for persons with altered immunocompetence. *MMWR Recomm. Rep.* 1993;42:1-18.

88. Welch PG, Fattom A, Moore J, Jr., et al. Safety and immunogenicity of Staphylococcus aureus type 5 capsular polysaccharide-Pseudomonas aeruginosa recombinant exoprotein A conjugate vaccine in patients on hemodialysis. *J. Am. Soc. Nephrol.* 1996;7:247-253.

89. Fattom A, Fuller S, Propst M, et al. Safety and immunogenicity of a booster dose of Staphylococcus aureus types 5 and 8 capsular polysaccharide conjugate vaccine (StaphVAX®) in hemodialysis patients. *Vaccine.* 2004;23:656-663.

90. Shinefield H, Black S, Fattom A, et al. Use of a Staphylococcus aureus Conjugate Vaccine in Patients Receiving Hemodialysis. *N. Engl. J. Med.* 2002;346:491-496.

91. Bagnoli F, Bertholet S, Grandi G. Inferring Reasons for the Failure of Staphylococcus aureus Vaccines in Clinical Trials. *Frontiers in Cellular and Infection Microbiology.* 2012;2:16.

92. Doebbeling BN. Nasal and hand carriage of Staphylococcus aureus in healthcare workers. *J. Chemother.* 1994;6 Suppl 2:11-17.

93. Yu VL, Goetz A, Wagener M, et al. Staphylococcus aureus nasal carriage and infection in patients on hemodialysis. Efficacy of antibiotic prophylaxis. *N. Engl. J. Med.* 1986;315:91-96.

94. Davies SJ, Ogg CS, Cameron JS, Poston S, Noble WC. Staphylococcus aureus nasal carriage, exit-site infection and catheter loss in patients treated with continuous ambulatory peritoneal dialysis (CAPD). *Perit. Dial. Int.* 1989;9:61-64.

95. Goldblum SE, Ulrich JA, Goldman RS, Reed WP. Nasal and cutaneous flora among hemodialysis patients and personnel: quantitative and qualitative characterization and patterns of Staphylococcal carriage. *Am. J. Kidney Dis.* 1982;2:281-286.

96. Boelaert JR, Van Landuyt HW, Gordts BZ, De Baere YA, Messer SA, Herwaldt LA. Nasal and Cutaneous Carriage of Staphylococcus aureus in Hemodialysis Patients: The Effect of Nasal Mupirocin. *Infection Control & Hospital Epidemiology.* 2015;17:809-811.

97. Luzar MA, Coles GA, Faller B, et al. Staphylococcus aureus Nasal Carriage and Infection in Patients on Continuous Ambulatory Peritoneal Dialysis. *N. Engl. J. Med.* 1990;322:505-509.

98. Kirmani N, Tuazon CU, Murray HW, Parrish AE, Sheagren JN. Staphylococcus aureus carriage rate of patients receiving long-term hemodialysis. *Arch. Intern. Med.* 1978;138:1657-1659.

99. Zimakoff J, Pedersen FB, Bergen L, et al. Staphylococcus aureus carriage and infections among patients in four haemo- and peritoneal-dialysis centres in Denmark. *J. Hosp. Infect.* 1996;33:289-300.

100. Emonts M, Uitterlinden AG, Nouwen JL, et al. Host Polymorphisms in Interleukin 4, Complement Factor H, and C-Reactive Protein Associated with Nasal Carriage of Staphylococcus aureus and Occurrence of Boils. *The Journal of Infectious Diseases.* 2008;197:1244-1253.

101. Wertheim HFL, Vos MC, Ott A, et al. Risk and outcome of nosocomial Staphylococcus aureus bacteraemia in nasal carriers versus non-carriers. *The Lancet.* 2004;364:703-705.

102. Hamdan-Partida A, Sainz-Espuñes T, Bustos-Martínez J. Characterization and Persistence of Staphylococcus aureus Strains Isolated from the Anterior Nares and Throats of Healthy Carriers in a Mexican Community. *J. Clin. Microbiol.* 2010;48:1701-1705.

103. Gorwitz RJ, Kruszon-Moran D, McAllister SK, et al. Changes in the Prevalence of Nasal Colonization with Staphylococcus aureus in the United States, 2001–2004. *The Journal of Infectious Diseases.* 2008;197:1226-1234.

104. Boelaert JR, De Smedt RA, De Baere YA, et al. The Influence of Calcium Mupirocin Nasal Ointment on the Incidence of Staphylococcus Aureus Infections in Haemodialysis Patients. *Nephrology Dialysis Transplantation.* 1989;4:278-281.

105. Boelaert JR, Van Landuyt HW, Godard CA, et al. Nasal mupirocin ointment decreases the incidence of Staphylococcus aureus bacteraemias in haemodialysis patients. *Nephrol. Dial. Transplant.* 1993;8:235-239.

106. Kluytmans JA, Manders MJ, van Bommel E, Verbrugh H. Elimination of nasal carriage of Staphylococcus aureus in hemodialysis patients. *Infect. Control Hosp. Epidemiol.* 1996;17:793-797.

107. Mupirocin Study Group. Nasal mupirocin prevents Staphylococcus aureus exit-site infection during peritoneal dialysis. . *J. Am. Soc. Nephrol.* 1996;7:2403-2408.

108. Bommer J, Vergetis W, Andrassy K, Hingst V, Borneff M, Huber W. Elimination of Staphylococcus aureus in hemodialysis patients. *ASAIO J.* 1995;41:127-131.

109. Johnson DW, MacGinley R, Kay TD, et al. A randomized controlled trial of topical exit site mupirocin application in patients with tunnelled, cuffed haemodialysis catheters. *Nephrol. Dial. Transplant.* 2002;17:1802-1807.

110. Teo BW, Low SJ, Ding Y, Koh TH, Hsu LY. High prevalence of mupirocin-resistant staphylococci in a dialysis unit where mupirocin and chlorhexidine are routinely used for prevention of catheter-related infections. *J. Med. Microbiol.* 2011;60:865-867.

111. Lobbedez T, Gardam M, Dedier H, et al. Routine use of mupirocin at the peritoneal catheter exit site and mupirocin resistance: still low after 7 years. *Nephrology Dialysis Transplantation.* 2004;19:3140-3143.

112. Al-Hwiesh AK, Abdul-Rahman IS, Al-Muhanna FA, Al-Sulaiman MH, Al-Jondebi MS, Divino-Filho JC. Prevention of peritoneal dialysis catheter infections in Saudi peritoneal dialysis patients: the emergence of high-level mupirocin resistance. *Int. J. Artif. Organs.* 2013;36:473-483.

113. Deshpande LM, Fix AM, Pfaller MA, Jones RN. Emerging elevated mupirocin resistance rates among staphylococcal isolates in the SENTRY Antimicrobial Surveillance Program (2000): correlations of results from disk diffusion, Etest and reference dilution methods. *Diagn. Microbiol. Infect. Dis.* 2002;42:283-290.

114. Annigeri R, Conly J, Vas S, et al. Emergence of mupirocin-resistant Staphylococcus aureus in chronic peritoneal dialysis patients using mupirocin prophylaxis to prevent exit-site infection. *Perit. Dial. Int.* 2001;21:554-559.

115. Lok CE, Stanley KE, Hux JE, Richardson R, Tobe SW, Conly J. Hemodialysis infection prevention with polysporin ointment. *J. Am. Soc. Nephrol.* 2003;14:169-179.

116. Johnson DW, van Eps C, Mudge DW, et al. Randomized, controlled trial of topical exit-site application of honey (Medihoney) versus mupirocin for the prevention of catheter-associated infections in hemodialysis patients. *J. Am. Soc. Nephrol.* 2005;16:1456-1462.

117. Bernardini J, Piraino B, Holley J, Johnston JR, Lutes R. A randomized trial of Staphylococcus aureus prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. *Am. J. Kidney Dis.* 1996;27:695-700.

118. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the Management of Intravascular Catheter-Related Infections. *Clin. Infect. Dis.* 2001;32:1249-1272.

119. Mermel LA. What Is The Predominant Source of Intravascular Catheter Infections? *Clin. Infect. Dis.* 2011;52:211-212.
120. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW. A Meta-analysis of Hemodialysis Catheter Locking Solutions in the Prevention of Catheter-Related Infection. *Am. J. Kidney Dis.* 2008;51:233-241.
121. Betjes MGH, van Agteren M. Prevention of dialysis catheter-related sepsis with a citrate–taurolidine-containing lock solution. *Nephrology Dialysis Transplantation.* 2004;19:1546-1551.
122. Dogra GK, Herson H, Hutchison B, et al. Prevention of tunneled hemodialysis catheter-related infections using catheter-restricted filling with gentamicin and citrate: a randomized controlled study. *J. Am. Soc. Nephrol.* 2002;13:2133-2139.
123. McIntyre CW, Hulme LJ, Taal M, Fluck RJ. Locking of tunneled hemodialysis catheters with gentamicin and heparin. *Kidney Int.* 2004;66:801-805.
124. Saxena AK, Panhotra BR, Sundaram DS, et al. Tunneled catheters' outcome optimization among diabetics on dialysis through antibiotic-lock placement. *Kidney Int.* 2006;70:1629-1635.
125. Weijmer MC, van den Dorpel MA, Van de Ven PJ, et al. Randomized, clinical trial comparison of trisodium citrate 30% and heparin as catheter-locking solution in hemodialysis patients. *J. Am. Soc. Nephrol.* 2005;16:2769-2777.
126. Kim SH, Song KI, Chang JW, et al. Prevention of uncuffed hemodialysis catheter-related bacteremia using an antibiotic lock technique: a prospective, randomized clinical trial. *Kidney Int.* 2006;69:161-164.
127. Nori US, Manoharan A, Yee J, Besarab A. Comparison of low-dose gentamicin with minocycline as catheter lock solutions in the prevention of catheter-related bacteremia. *Am. J. Kidney Dis.* 2006;48:596-605.
128. Moore CL, Besarab A, Ajluni M, et al. Comparative effectiveness of two catheter locking solutions to reduce catheter-related bloodstream infection in hemodialysis patients. *Clin. J. Am. Soc. Nephrol.* 2014;9:1232-1239.
129. Allon M. Prophylaxis against dialysis catheter-related bacteremia with a novel antimicrobial lock solution. *Clin. Infect. Dis.* 2003;36:1539-1544.
130. Allon M. Dialysis catheter-related bacteremia: treatment and prophylaxis. *Am. J. Kidney Dis.* 2004;44:779-791.
131. Saad TF. Bacteremia associated with tunneled, cuffed hemodialysis catheters. *Am. J. Kidney Dis.* 1999;34:1114-1124.
132. Eleftheriadis T, Liakopoulos V, Leivaditis K, Antoniadi G, Stefanidis I. Infections in hemodialysis: a concise review - Part 1: bacteremia and respiratory infections. *Hippokratia.* 2011;15:12-17.
133. Allon M. Current management of vascular access. *Clin. J. Am. Soc. Nephrol.* 2007;2:786-800.
134. Treter J, Macedo A. *Catheters: A suitable surface for biofilm formation*2011.
135. Donlan RM. Biofilms and device-associated infections. *Emerg. Infect. Dis.* 2001;7:277-281.
136. Stowe S, J Richards J, T Tucker A, Thompson R, Melander C, Cavanagh J. *Anti-Biofilm Compounds Derived from Marine Sponges*2011.
137. Bjarnsholt T. The role of bacterial biofilms in chronic infections. *APMIS Suppl.* 2013:1-51.

138. Gominet M, Compain F, Beloin C, Lebeaux D. Central venous catheters and biofilms: where do we stand in 2017? *APMIS.* 2017;125:365-375.
139. Lebeaux D, Ghigo J-M, Beloin C. Biofilm-Related Infections: Bridging the Gap between Clinical Management and Fundamental Aspects of Recalcitrance toward Antibiotics. *Microbiology and Molecular Biology Reviews : MMBR.* 2014;78:510-543.
140. Khardori N, Yassien M. Biofilms in device-related infections. *J. Ind. Microbiol.* 1995;15:141-147.
141. Anderl JN, Franklin MJ, Stewart PS. Role of Antibiotic Penetration Limitation in Klebsiella pneumoniae Biofilm Resistance to Ampicillin and Ciprofloxacin. *Antimicrob. Agents Chemother.* 2000;44:1818-1824.
142. Balaban NQ, Merrin J, Chait R, Kowalik L, Leibler S. Bacterial persistence as a phenotypic switch. *Science.* 2004;305:1622-1625.
143. Shah D, Zhang Z, Khodursky A, Kaldalu N, Kurg K, Lewis K. Persisters: a distinct physiological state of E. coli. *BMC Microbiol.* 2006;6:53-53.
144. Clinical Practice Guidelines for Vascular Access. *Am. J. Kidney Dis.* 2006;48:S248-S273.
145. Ashby DR, Power A, Singh S, et al. Bacteremia associated with tunneled hemodialysis catheters: outcome after attempted salvage. *Clin. J. Am. Soc. Nephrol.* 2009;4:1601-1605.
146. Schwab SJ, Buller GL, McCann RL, Bollinqer RR, Stickel DL. Prospective Evaluation of a Dacron Cuffed Hemodialysis Catheter for Prolonged Use. *Am. J. Kidney Dis.*;11:166-169.
147. Moss AH, Vasilakis C, Holley JL, Foulks CJ, Pillai K, McDowell DE. Use of a silicone dual-lumen catheter with a Dacron cuff as a long-term vascular access for hemodialysis patients. *Am. J. Kidney Dis.* 1990;16:211-215.
148. Hasan J, Crawford RJ, Ivanova EP. Antibacterial surfaces: the quest for a new generation of biomaterials. *Trends Biotechnol.* 2013;31:295-304.
149. El Habnouni S, Lavigne JP, Darcos V, et al. Toward potent antibiofilm degradable medical devices: a generic method for the antibacterial surface modification of polylactide. *Acta biomaterialia.* 2013;9:7709-7718.
150. Campoccia D, Montanaro L, Arciola CR. A review of the clinical implications of anti-infective biomaterials and infection-resistant surfaces. *Biomaterials.* 2013;34:8018-8029.
151. Busscher HJ, van der Mei HC, Subbiahdoss G, et al. Biomaterial-associated infection: locating the finish line in the race for the surface. *Sci. Transl. Med.* 2012;4:153rv110.
152. Cegelski L, Pinkner JS, Hammer ND, et al. Small-molecule inhibitors target Escherichia coli amyloid biogenesis and biofilm formation. *Nat. Chem. Biol.* 2009;5:913-919.
153. Cusumano CK, Pinkner JS, Han Z, et al. Treatment and Prevention of Urinary Tract Infection with Orally Active FimH Inhibitors. *Sci. Transl. Med.* 2011;3:109ra115-109ra115.
154. Ammons MC, Ward LS, James GA. Anti-biofilm efficacy of a lactoferrin/xylitol wound hydrogel used in combination with silver wound dressings. *International wound journal.* 2011;8:268-273.
155. Pflumm M. Caught on film. *Nat. Med.* 2011;17:650-653.

156. Reid G, Howard J, Gan BS. Can bacterial interference prevent infection? *Trends Microbiol.* 2001;9:424-428.
157. Klemm P, Hancock V, Schembri MA. Mellowing Out: Adaptation to Commensalism by Escherichia coli Asymptomatic Bacteriuria Strain 83972. *Infect. Immun.* 2007;75:3688-3695.
158. Sunden F, Hakansson L, Ljunggren E, Wullt B. Escherichia coli 83972 bacteriuria protects against recurrent lower urinary tract infections in patients with incomplete bladder emptying. *J. Urol.* 2010;184:179-185.
159. Donlan RM. Biofilm elimination on intravascular catheters: important considerations for the infectious disease practitioner. *Clin. Infect. Dis.* 2011;52:1038-1045.
160. Doolittle MM, Cooney JJ, Caldwell DE. Lytic infection of Escherichia coli biofilms by bacteriophage T4. *Can. J. Microbiol.* 1995;41:12-18.
161. Davies DG, Marques CNH. A Fatty Acid Messenger Is Responsible for Inducing Dispersion in Microbial Biofilms. *J. Bacteriol.* 2009;191:1393-1403.
162. Conlon BP, Nakayasu ES, Fleck LE, et al. Killing persister cells and eradicating a biofilm infection by activating the ClpP protease. *Nature.* 2013;503:365-370.
163. Morones-Ramirez JR, Winkler JA, Spina CS, Collins JJ. Silver Enhances Antibiotic Activity Against Gram-negative Bacteria. *Sci. Transl. Med.* 2013;5:190ra181-190ra181.
164. Barraud N, Buson A, Jarolimek W, Rice SA. Mannitol Enhances Antibiotic Sensitivity of Persister Bacteria in Pseudomonas aeruginosa Biofilms. *PLoS One.* 2013;8:e84220.
165. Krishnasami Z, Carlton D, Bimbo L, et al. Management of hemodialysis catheter-related bacteremia with an adjunctive antibiotic lock solution. *Kidney Int.* 2002;61:1136-1142.
166. Poole CV, Carlton D, Bimbo L, Allon M. Treatment of catheter-related bacteraemia with an antibiotic lock protocol: effect of bacterial pathogen. *Nephrol. Dial. Transplant.* 2004;19:1237-1244.
167. Vardhan A, Davies J, Daryanani I, Crowe A, McClelland P. Treatment of haemodialysis catheter-related infections. *Nephrology Dialysis Transplantation.* 2002;17:1149-1150.
168. Falagas ME, Fragoulis KN, Bliziotis IA. Oral rifampin for prevention of S. aureus carriage-related infections in patients with renal failure—a meta-analysis of randomized controlled trials. *Nephrology Dialysis Transplantation.* 2006;21:2536-2542.
169. Falagas ME, Bliziotis IA, Fragoulis KN. Oral rifampin for eradication of Staphylococcus aureus carriage from healthy and sick populations: A systematic review of the evidence from comparative trials. *Am. J. Infect. Control.* 2007;35:106-114.
170. Atkinson BA, Lorian V. Antimicrobial agent susceptibility patterns of bacteria in hospitals from 1971 to 1982. *J. Clin. Microbiol.* 1984;20:791-796.
171. Stapleton PD, Taylor PW. Methicillin resistance in Staphylococcus aureus: mechanisms and modulation. *Sci. Prog.* 2002;85:57-72.
172. Aeilts GD, Sapico FL, Canawati HN, Malik GM, Montgomerie JZ. Methicillin-resistant-Staphylococcus aureus colonization and infection in a rehabilitation facility. *J. Clin. Microbiol.* 1982;16:218-223.

173. Blackwell CC, Feingold DS. Frequency and some properties of clinical isolates of methicillin-resistant Staphylococcus aureus. *Am. J. Clin. Pathol.* 1975;64:372-377.
174. Panlilio AL, Culver DH, Gaynes RP, et al. Methicillin-resistant Staphylococcus aureus in U.S. hospitals, 1975-1991. *Infect. Control Hosp. Epidemiol.* 1992;13:582-586.
175. Boyce JM, Causey WA. Increasing occurrence of methicillin-resistant Staphylococcus aureus in the United States. *Infect. Control.* 1982;3:377-383.
176. Crossley K, Loesch D, Landesman B, Mead K, Chern M, Strate R. An outbreak of infections caused by strains of Staphylococcus aureus resistant to methicillin and aminoglycosides. I. Clinical studies. *J. Infect. Dis.* 1979;139:273-279.
177. Schaefler S, Jones D, Perry W, et al. Emergence of gentamicin- and methicillin-resistant Staphylococcus aureus strains in New York City hospitals. *J. Clin. Microbiol.* 1981;13:754-759.
178. Buckwold FJ, Albritton WL, Ronald AR, Lertzman J, Henriksen R. Investigations of the Occurrence of Gentamicin-Resistant Staphylococcus aureus. *Antimicrob. Agents Chemother.* 1979;15:152-156.
179. Vogel L, Nathan C, Sweeney HM, Kabins SA, Cohen S. Infections due to gentamicin-resistant Staphylococcus aureus strain in a nursery for neonatal infants. *Antimicrob. Agents Chemother.* 1978;13:466-472.
180. Kauffman CA, Ramundo NC, Williams SG, Dey CR, Phair JP, Watanakunakorn C. Surveillance of Gentamicin-Resistant Gram-Negative Bacilli in a General Hospital. *Antimicrob. Agents Chemother.* 1978;13:918-923.
181. Maliwan N, Grieble HG, Bird TJ. Hospital Pseudomonas aeruginosa: Surveillance of Resistance to Gentamicin and Transfer of Aminoglycoside R Factor. *Antimicrob. Agents Chemother.* 1975;8:415-420.
182. Minshew BH, Pollock HM, Schoenknecht FD, Sherris JC. Emergence in a Burn Center of Populations of Bacteria Resistant to Gentamicin, Tobramycin, and Amikacin: Evidence for the Need for Changes in Zone Diameter Interpretative Standards. *Antimicrob. Agents Chemother.* 1977;12:688-696.
183. Preheim LC, Penn RG, Sanders CC, Goering RV, Giger DK. Emergence of resistance to beta-lactam and aminoglycoside antibiotics during moxalactam therapy of Pseudomonas aeruginosa infections. *Antimicrob. Agents Chemother.* 1982;22:1037-1041.
184. Srinivasan A, Dick JD, Perl TM. Vancomycin Resistance in Staphylococci. *Clin. Microbiol. Rev.* 2002;15:430-438.
185. Johnson AP, Uttley AH, Woodford N, George RC. Resistance to vancomycin and teicoplanin: an emerging clinical problem. *Clin. Microbiol. Rev.* 1990;3:280-291.
186. Lok CE, Mokrzycki MH. Prevention and management of catheter-related infection in hemodialysis patients. *Kidney Int.* 2011;79:587-598.
187. Katneni R, Hedayati SS. Central venous catheter-related bacteremia in chronic hemodialysis patients: epidemiology and evidence-based management. *Nat. Clin. Pract. Nephrol.* 2007;3:256-266.
188. Fitzgibbons LN, Puls DL, Mackay K, Forrest GN. Management of gram-positive coccal bacteremia and hemodialysis. *Am. J. Kidney Dis.* 2011;57:624-640.
189. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in Staphylococcus aureus. *Emerg. Infect. Dis.* 2001;7:327-332.

190. Sieradzki K, Roberts RB, Haber SW, Tomasz A. The Development of Vancomycin Resistance in a Patient with Methicillin-Resistant Staphylococcus aureus Infection. *N. Engl. J. Med.* 1999;340:517-523.
191. Chang S, Sievert DM, Hageman JC, et al. Infection with Vancomycin-Resistant Staphylococcus aureus Containing the vanA Resistance Gene. *N. Engl. J. Med.* 2003;348:1342-1347.
192. Schwalbe RS, Stapleton JT, Gilligan PH. Emergence of Vancomycin Resistance in Coagulase-Negative Staphylococci. *N. Engl. J. Med.* 1987;316:927-931.
193. Veach LA, Pfaller MA, Barrett M, Koontz FP, Wenzel RP. Vancomycin resistance in Staphylococcus haemolyticus causing colonization and bloodstream infection. *J. Clin. Microbiol.* 1990;28:2064-2068.
194. Werner G, Coque TM, Hammerum AM, et al. Emergence and spread of vancomycin resistance among enterococci in Europe. *Eurosurveillance.* 2008;13:19046.
195. Mittal S, Singla P, Deep A, et al. Vancomycin and High Level Aminoglycoside Resistance in Enterococcus spp. in a Tertiary Health Care Centre: A Therapeutic Concern. *Journal of Pathogens.* 2016;2016:8262561.
196. Kawalec M, Gniadkowski M, Zaleska M, Ozorowski T, Konopka L, Hryniewicz W. Outbreak of Vancomycin-Resistant Enterococcus faecium of the Phenotype VanB in a Hospital in Warsaw, Poland: Probable Transmission of the Resistance Determinants into an Endemic Vancomycin-Susceptible Strain. *J. Clin. Microbiol.* 2001;39:1781-1787.
197. Harthug S, Digranes A, Hope O, Kristiansen BE, Allum AG, Langeland N. Vancomycin resistance emerging in a clonal outbreak caused by ampicillin-resistant Enterococcus faecium. *Clin. Microbiol. Infect.* 2000;6:19-28.
198. Murray BE. Vancomycin-Resistant Enterococcal Infections. *N. Engl. J. Med.* 2000;342:710-721.
199. Rice LB. Emergence of vancomycin-resistant enterococci. *Emerg. Infect. Dis.* 2001;7:183-187.
200. Howden BP, Johnson PDR, Ward PB, Stinear TP, Davies JK. Isolates with Low-Level Vancomycin Resistance Associated with Persistent Methicillin-Resistant Staphylococcus aureus Bacteremia. *Antimicrob. Agents Chemother.* 2006;50:3039-3047.
201. McGuinness WA, Malachowa N, DeLeo FR. Vancomycin Resistance in Staphylococcus aureus *The Yale Journal of Biology and Medicine.* 2017;90:269-281.
202. Périchon B, Courvalin P. VanA-Type Vancomycin-Resistant Staphylococcus aureus. *Antimicrob. Agents Chemother.* 2009;53:4580-4587.
203. Foucault M-L, Courvalin P, Grillot-Courvalin C. Fitness Cost of VanA-Type Vancomycin Resistance in Methicillin-Resistant Staphylococcus aureus. *Antimicrob. Agents Chemother.* 2009;53:2354-2359.
204. Recommendations for preventing the spread of vancomycin resistance: recommendations of the Hospital Infection Control Practices Advisory Committee (HICPAC). *Am. J. Infect. Control.* 1995;23:87-94.
205. DeLisle S, Perl TM. Vancomycin-Resistant Enterococci*: A Road Map on How To Prevent the Emergence and Transmission of Antimicrobial Resistance. *Chest.* 2003;123:504S-518S.

206. Chavers BM, Solid CA, Gilbertson DT, Collins AJ. Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. *J. Am. Soc. Nephrol.* 2007;18:952-959.
207. Rayner HC, Pisoni RL, Bommer J, et al. Mortality and hospitalization in haemodialysis patients in five European countries: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol. Dial. Transplant.* 2004;19:108-120.
208. Allon M, Radeva M, Bailey J, et al. The spectrum of infection-related morbidity in hospitalized haemodialysis patients. *Nephrology Dialysis Transplantation.* 2005;20:1180-1186.
209. Powe NR, Jaar B, Furth SL, Hermann J, Briggs W. Septicemia in dialysis patients: Incidence, risk factors, and prognosis. *Kidney Int.*;55:1081-1090.
210. Shah BR, Hux JE. Quantifying the Risk of Infectious Diseases for People With Diabetes. *Diabetes Care.* 2003;26:510.
211. Nissenson AR, Dylan ML, Griffiths RI, Yu HT, Dubois RW. Septicemia in patients with ESRD is associated with decreased hematocrit and increased use of erythropoietin. *Clin. J. Am. Soc. Nephrol.* 2006;1:505-510.
212. Blayney MJ, Pisoni RL, Bragg-Gresham JL, et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. *Kidney Int.* 2008;74:655-663.
213. Ng P, Wong H, Lyon D, et al. Combined use of alcohol hand rub and gloves reduces the incidence of late onset infection in very low birthweight infants. *Archives of Disease in Childhood Fetal and Neonatal Edition.* 2004;89:F336-F340.
214. Hilburn J, Hammond BS, Fendler EJ, Groziak PA. Use of alcohol hand sanitizer as an infection control strategy in an acute care facility. *Am. J. Infect. Control.* 2003;31:109-116.
215. Chakravarthy M, Adhikary R, Gokul B, Pushparaj L. Hospital acquired infection is inversely related to utilization of isopropyl alcohol and tissue paper pulls--a prospective observational study. *J. Assoc. Physicians India.* 2011;59:548-550.
216. Rosenthal VD, Guzman S, Safdar N. Reduction in nosocomial infection with improved hand hygiene in intensive care units of a tertiary care hospital in Argentina. *Am. J. Infect. Control.* 2005;33:392-397.
217. Swenson BR, Hedrick TL, Metzger R, Bonatti H, Pruett TL, Sawyer RG. Effects of Preoperative Skin Preparation on Postoperative Wound Infection Rates: A Prospective Study of 3 Skin Preparation Protocols. *Infect. Control Hosp. Epidemiol.* 2009;30:964-971.
218. Borges LFdAe, Rocha LA, Nunes MJ, Gontijo Filho PP. Low Compliance to Handwashing Program and High Nosocomial Infection in a Brazilian Hospital. *Interdiscip. Perspect. Infect. Dis.* 2012;2012:579681.
219. Davis CR. Infection-free surgery: how to improve hand-hygiene compliance and eradicate methicillin-resistant Staphylococcus aureus from surgical wards. *Ann. R. Coll. Surg. Engl.* 2010;92:316-319.
220. Gould D, Chamberlain A. The use of ward-based educational teaching package to enhance nurses compliance with infection control procedures. *J. Clin. Nurs.* 1997;6.
221. Helder OK, Brug J, Looman CW, van Goudoever JB, Kornelisse RF. The impact of an education program on hand hygiene compliance and nosocomial infection incidence in

an urban neonatal intensive care unit: an intervention study with before and after comparison. *Int. J. Nurs. Stud.* 2010;47:1245-1252.

222. Aboumatar H, Ristaino P, Davis RO, et al. Infection prevention promotion program based on the PRECEDE model: improving hand hygiene behaviors among healthcare personnel. *Infect. Control Hosp. Epidemiol.* 2012;33:144-151.

223. Stone PW, Pogorzelska M, Kunches L, Hirschhorn LR. Hospital Staffing and Health Care–Associated Infections: A Systematic Review of the Literature. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2008;47:937-944.

224. Blot SI, Serra ML, Koulenti D, et al. Patient to nurse ratio and risk of ventilator-associated pneumonia in critically ill patients. *Am. J. Crit. Care.* 2011;20:e1-9.

225. West E, Barron DN, Harrison D, Rafferty AM, Rowan K, Sanderson C. Nurse staffing, medical staffing and mortality in Intensive Care: An observational study. *Int. J. Nurs. Stud.* 2014;51:781-794.

226. Rogowski JA, Staiger D, Patrick T, Horbar J, Kenny M, Lake ET. Nurse staffing and NICU infection rates. *JAMA Pediatr.* 2013;167:444-450.

227. Cimiotti JP, Aiken LH, Sloane DM, Wu ES. Nurse staffing, burnout, and health care-associated infection. *Am. J. Infect. Control.* 2012;40:486-490.

228. Institute of Medicine Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing atIoM. *The Future of Nursing: Leading Change, Advancing Health*. Washington (DC): National Academies Press (US)

229. Romanow RJ. Building on Values: The Future of Health Care in Canada – Final Report. Ottawa, ON: Commission on the Future of Health Care in Canada; 2002.

230. Shang J, Stone P, Larson E. Studies on Nurse staffing and Healthcare Associated Infection: Methodological Challenges and Potential Solutions. *Am. J. Infect. Control.* 2015;43:581-588.

231. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA.* 2002;288.

232. Shindul-Rothschild J, Berry D, Long-Middleton E. Where Have All The Nurses Gone? Final Results of AJN's Patient Care Survey. *MCN: The American Journal of Maternal/Child Nursing.* 1997;22:33-47.

233. Aiken LH, Clarke SP, Sloane DM, et al. Nurses' reports on hospital care in five countries. *Health Aff. (Millwood).* 2001;20:43-53.

234. Hugonnet S, Chevrolet JC, Pittet D. The effect of workload on infection risk in critically ill patients. *Crit. Care Med.* 2007;35:76-81.

235. Amaravadi RK, Dimick JB, Pronovost PJ, Lipsett PA. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. *Intensive Care Med.* 2000;26:1857-1862.

236. Pronovost PJ, Dang D, Dorman T, et al. Intensive care unit nurse staffing and the risk for complications after abdominal aortic surgery. *Eff. Clin. Pract.* 2001;4:199-206.

237. Fridkin SK, Pear SM, Williamson TH, Galgiani JN, Jarvis WR. The role of understaffing in central venous catheter-associated bloodstream infections. *Infect. Control Hosp. Epidemiol.* 1996;17:150-158.

238. Hugonnet S, Uçkay I, Pittet D. *Staffing level: a determinant of late-onset ventilator-associated pneumonia*. *Critical Care.* 2007;11:R80-R80.

239. Borg MA. Bed occupancy and overcrowding as determinant factors in the incidence of MRSA infections within general ward settings. *J. Hosp. Infect.* 2003;54:316-318.
240. Conly JM, Hill S, Ross J, Lertzman J, Louie TJ. Handwashing practices in an intensive care unit: the effects of an educational program and its relationship to infection rates. *Am. J. Infect. Control.* 1989;17:330-339.
241. Gopal Rao G, Jeanes A, Osman M, Aylott C, Green J. Marketing hand hygiene in hospitals--a case study. *J. Hosp. Infect.* 2002;50:42-47.
242. Lafrance JP, Rahme E, Iqbal S, et al. Association of dialysis modality with risk for infection-related hospitalization: a propensity score-matched cohort analysis. *Clin. J. Am. Soc. Nephrol.* 2012;7:1598-1605.
243. Cimiotti JP, Haas J, Saiman L, Larson EL. Impact of staffing on bloodstream infections in the neonatal intensive care unit. *Arch. Pediatr. Adolesc. Med.* 2006;160:832-836.
244. Stegenga J, Bell E, Matlow A. The role of nurse understaffing in nosocomial viral gastrointestinal infections on a general pediatrics ward. *Infect. Control Hosp. Epidemiol.* 2002;23:133-136.
245. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: fitting a model to the data. *J. Infect. Dis.* 2002;185:481-488.
246. Christine K, Cheryl J, Chunliu Z, Peter JG, Jayasree B. Nurse Staffing and Postsurgical Adverse Events: An Analysis of Administrative Data from a Sample of U.S. Hospitals, 1990–1996. *Health Serv. Res.* 2002;37:611-629.
247. Stone PW, Mooney-Kane C, Larson EL, et al. Nurse working conditions and patient safety outcomes. *Med. Care.* 2007;45:571-578.
248. Arenas MD, Sánchez-Payá J, Barril G, et al. A multicentric survey of the practice of hand hygiene in haemodialysis units: factors affecting compliance. *Nephrology Dialysis Transplantation.* 2005;20:1164-1171.
249. Glance LG, Dick AW, Osler TM, Mukamel DB, Li Y, Stone PW. The association between nurse staffing and hospital outcomes in injured patients. *BMC Health Serv. Res.* 2012;12:247.
250. Dimick JB, Swoboda SM, Pronovost PJ, Lipsett PA. Effect of nurse-to-patient ratio in the intensive care unit on pulmonary complications and resource use after hepatectomy. *American journal of critical care : an official publication, American Association of Critical-Care Nurses.* 2001;10:376-382.
251. Kovner C, Gergen PJ. Nurse staffing levels and adverse events following surgery in U.S. hospitals. *Image J. Nurs. Sch.* 1998;30:315-321.
252. Whitman GR, Kim Y, Davidson LJ, Wolf GA, Wang SL. The impact of staffing on patient outcomes across specialty units. *J. Nurs. Adm.* 2002;32:633-639.
253. Rastogi A, Chertow GM. Mandating Staffing Ratios in Hemodialysis Facilities: California SB 349 and Unintended Consequences. *Clin. J. Am. Soc. Nephrol.* 2018.
254. Hugonnet S, Harbarth S, Sax H, Duncan RA, Pittet D. Nursing resources: a major determinant of nosocomial infection? *Arch. Pediatr. Adolesc. Med.* 2006;160:832-836.
255. Owen WFJ, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The Urea Reduction Ratio and Serum Albumin Concentration as Predictors of Mortality in Patients Undergoing Hemodialysis. *N. Engl. J. Med.* 1993;329:1001-1006.

256. Dalrymple LS, Johansen KL, Chertow GM, et al. Infection-Related Hospitalizations in Older Patients With End-Stage Renal Disease. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2010;56:522-530.
257. Dalrymple LS, Katz R, Kestenbaum B, et al. The Risk of Infection-Related Hospitalization With Decreased Kidney Function. *Am. J. Kidney Dis.* 2012;59:356-363.
258. James MT, Laupland KB, Tonelli M, et al. Risk of bloodstream infection in patients with chronic kidney disease not treated with dialysis. *Arch. Intern. Med.* 2008;168:2333-2339.
259. Lopes AA, Bragg-Gresham JL, Elder SJ, et al. Independent and joint associations of nutritional status indicators with mortality risk among chronic hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS). *J. Ren. Nutr.* 2010;20:224-234.
260. Pifer TB, McCullough KP, Port FK, et al. Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int.* 2002;62:2238-2245.
261. Hoen B, Paul-Dauphin A, Hestin D, Kessler M. EPIBACDIAL: a multicenter prospective study of risk factors for bacteremia in chronic hemodialysis patients. *J. Am. Soc. Nephrol.* 1998;9:869-876.
262. Roberts TL, Obrador GT, St. Peter WL, Pereira BJG, Collins AJ. Relationship among catheter insertions, vascular access infections, and anemia management in hemodialysis patients. *Kidney Int.* 2004;66:2429-2436.
263. Azar AT, Wahba K, Mohamed AS, Massoud WA. Association between dialysis dose improvement and nutritional status among hemodialysis patients. *Am. J. Nephrol.* 2007;27:113-119.
264. Schommer NN, Gallo RL. Structure and function of the human skin microbiome. *Trends Microbiol.* 2013;21:660-668.
265. James G, Swogger E, deLancey-Pulcini E. Microbial Ecology of Human Skin and Wounds. In: Shirtliff M, Leid JG, eds. *The Role of Biofilms in Device-Related Infections*. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009:1-14.
266. Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings: Recommendations of the healthcare infection control practices advisory committee and the hicpac/shea/apic/idsa hand hygiene task force. *Am. J. Infect. Control.* 2002;30:S1-S46.
267. Mathur P. Hand hygiene: Back to the basics of infection control. *The Indian Journal of Medical Research.* 2011;134:611-620.
268. Larson E. Skin Hygiene and Infection Prevention: More of the Same or Different Approaches? *Clin. Infect. Dis.* 1999;29:1287-1294.
269. Larson E. A causal link between handwashing and risk of infection? Examination of the evidence. *Infect. Control Hosp. Epidemiol.* 1988;9:28-36.
270. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Infection Control Program. *Ann. Intern. Med.* 1999;130.
271. Oliveira ACd, Gama CS, Paula AOd. Adherence and factors related to acceptance of alcohol for antiseptic hand rubbing among nursing professionals. *Rev. Esc. Enferm. USP.* 2017;51.
272. Pittet D. Hand Hygiene and patient care: pursuing the Semmelweis legacy. *Lancet Infect Dis*2001.

273. Nevo I, Fitzpatrick M, Thomas RE, et al. The efficacy of visual cues to improve hand hygiene compliance. *Simulation in healthcare : journal of the Society for Simulation in Healthcare.* 2010;5:325-331.
274. Birnbach DJ, Nevo I, Scheinman SR, Fitzpatrick M, Shekhter I, Lombard JL. Patient safety begins with proper planning: a quantitative method to improve hospital design. *Quality & safety in health care.* 2010;19:462-465.
275. Thomas BW, Berg-Copas GM, Vasquez DG, Jackson BL, Wetta-Hall R. Conspicuous vs customary location of hand hygiene agent dispensers on alcohol-based hand hygiene product usage in an intensive care unit. *J. Am. Osteopath. Assoc.* 2009;109:263-267; quiz 280-261.
276. Zellmer C, Blakney R, Van Hoof S, Safdar N. Impact of sink location on hand hygiene compliance for Clostridium difficile infection. *Am. J. Infect. Control.* 2015;43:387-389.
277. Deyneko A, Cordeiro F, Berlin L, Ben-David D, Perna S, Longtin Y. Impact of sink location on hand hygiene compliance after care of patients with Clostridium difficile infection: a cross-sectional study. *BMC Infect. Dis.* 2016;16:203.
278. Kaplan LM, McGuckin M. Increasing handwashing compliance with more accessible sinks. *Infect. Control.* 1986;7:408-410.
279. Cloutman-Green E, Kalaycioglu O, Wojani H, et al. The important role of sink location in handwashing compliance and microbial sink contamination. *Am. J. Infect. Control.* 2014;42:554-555.
280. Whitby M, McLaws ML. *Handwashing in healthcare workers: Accessibility of sink location does not improve compliance*2005.
281. Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by health care workers: The impact of introducing an accessible, alcohol-based hand antiseptic. *Arch. Intern. Med.* 2000;160:1017-1021.
282. Haas JP, Larson EL. Impact of wearable alcohol gel dispensers on hand hygiene in an emergency department. *Acad. Emerg. Med.* 2008;15:393-396.
283. Giannitsioti E, Athanasia S, Antoniadou A, et al. Does a bed rail system of alcohol-based handrub antiseptic improve compliance of health care workers with hand hygiene? Results from a pilot study. *Am. J. Infect. Control.* 2009;37:160-163.
284. Boog MC, Erasmus V, de Graaf JM, van Beeck EHE, Melles M, van Beeck EF. Assessing the optimal location for alcohol-based hand rub dispensers in a patient room in an intensive care unit. *BMC Infect. Dis.* 2013;13:510-510.
285. Patel PR, Kallen AJ, Arduino MJ. Epidemiology, surveillance, and prevention of bloodstream infections in hemodialysis patients. *Am. J. Kidney Dis.* 2010;56:566-577.
286. Schwab SJ, Beathard G. The hemodialysis catheter conundrum: hate living with them, but can't live without them. *Kidney Int.* 1999;56:1-17.
287. Kaplowitz LG, Cornstock JA, Landwehr DM, Dalton HP, Mayhall CG. A Prospective Study of Infections in Hemodialysis Patients: Patient Hygiene and Other Risk Factors for Infection. *Infection Control & Hospital Epidemiology.* 1988;9:534-541.

Appendix I: ICD-9, ICD-10, RAMQ codes

Table of codes used to construct cohort of hemodialysis patients	
Hospital discharge diagnoses related to dialysis (Med-Echo)	V451, V560, V568, V569, E8791, E8702, E8712, E8722, E8742, Z490, Z491, Z492, Z992, Y602, Y612, Y622
Hospital procedure codes related to dialysis (Med-Echo)	5195, 6698, 1PZ21
RAMQ billing codes (related to dialysis)	00283-00290, 00147, 09259, 09260, 09261, 09274, 09275, 09216, 09217, 09218, 09219, 09262, 09279, 09263, 09264, 09291, 09382, 09383, 15035, 15036, 15040, 15041, 15042, 15043 15044, 15045, 15046, 15047, 15048 15050, 15051

Table 13. Hemodialysis codes

Definition	ICD-9 codes	ICD-10 codes	RAMQ procedure codes
Arrhythmia	427.0,427.1,427.2, 427.3, 427.4, 427.81	I47.2,I48.x ,I47.0, I47.1, I47.9, I49.0, I49.5	00631, 00632, 00662, 09302,
Cardiovascular disease	410.xx (except 410.x2), 411.xx, (except 411.0), 412.xx, 413.0, 413.9, 414.xx (except 414.1)	I21.x,I24.x (except I24.1), I25.x, I20.0, I20.9, I25.x (except I25.3 and I25.4)	09303, 04601-04606, 04860-04865
Cerebrovascular disease	435.xx, 430-432.xx, 434.xx,436.xx, 438.xx (342.xx, 433.xx, 435.xx, 438.xx), 433.xx+342.xx	G45.x, I60.x-I62.x, I64.x, I66.x, I69.x, I73.x, I63.3-I63.9, G46.0, G46.6, G46.7, (I65.x, I63.0-I63.2, I66.3)+Z50, (I65.x,I63.0-I63.2, I66.3)+G81.x, G81.x+Z50	
Chronic kidney disease	581.0-581.2, 581.81, 582.xx, 583.xx, 585.xx-587.xx, 403.x1, 404.x2, 404.x3, 247.10, 593.3, 593.4, 593.71-593.73, 753.12-753.16	N04.1-N04.7, N07.0, N05.x, N01.x, N14.x, N08.x, N03.x, N29.0, N16.3, N18.x,N19.x, N26.x, I12.x, I13.x, N13.0, N13.1, N13.5, N13.7, N13.8, N13.9, Q61.1-Q61.5	
Chronic pulmonary disease	492.xx, 493.xx, 496.xx	J43.x, J45.x, J44.x	
Chronic liver disease	070.xx, 571.xx, 572.2, 572.3, 572.4, 572.8	B15.x -B19.x, K70.x, K73.x, K74.x, K76.0, B15.0 ,B16.0, B16.2, B19.0, K76.6, K76.7, K70.4, K72.9, K77.8, K72.1	
Congestive heart failure	428.xx, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	I50.x I11+I50, I13+I50	
Diabetes	250.xx, 357.2, 362.0, 366.41	E10.x-E14.x, G63.2, H36.0, H28.0	
Hyperlipidemia	272.0-272.4x	E78.0-E78.5	
Hypertension	401-405.xx, 437.2, 997.91	I10.x-I15.x, I67.4	

Malignancy	140-209.xx (except 173.xx)	C00.x-C97.x (except C44.x, C46.0)	
Peripheral vascular disease (excludes renal and aorta)	250.7, 440.2, 440.3,440.8, 440.9, 443.xx, 785.4	E10.5, E11.5, E13.5,E14.5, I70.2, I70.8-I70.9, I73.x, R02	09494-09496, 04694-04699, 04707-04709, 04713-04720
Valvular disease	394.xx, 395.xx, 396.xx, 424.0-424.3	I05.x,I06.x, I08.X,I34.x,I39.0, I35.x,I36.x,I37.x, I39.1, I39.2,I39.3	

Table 14. Comorbidities codes

Definition	ICD-9 codes	ICD-10 codes
Infection (all)	001-134C3:D38, 136, 139, 254.1, 320-326, 331.81, 362, 372.0-372.3, 373.0-373.2, 382, 383.0, 386.33, 386.35, 388.60, 390-392, 421.0,421.1, 422.0, 422.91-422.93, 449, 460-466, 472-473, 474.0, 475, 476.0-476.1, 478.21-478.22, 478.24, 478.29, 480-488, 490, 491.1, 494, 510, 511.0-511.1, 513, 518.6, 519.01, 519.2,522.5, 522.7, 527.3, 528.3, 540-542, 562.01, 562.03, 562.10, 562.13, 566-567, 569.5, 572.0-572.1, 573.1-573.3, 575.0-575.1, 590, 595.0-595.4, 597, 598.0, 599.0, 601, 603.1, 604, 607.1-607.2, 608.0, 608.4, 611.0, 614-615, 616.0-616.1, 616.3-616.4, 616.8, 639.0, 646.6, 647, 670, 675, 680-686, 695.81, 706.0, 711, 727.89, 728.0, 730.0-730.3, 730.8-730.9, 780.60, 785.52, 790.7-790.8, 958.3, 996.6, 997.62, 998.5, 999.3	A00-A32, A34-A99, B00-B89, B95-B97, B99, D73.3, E32.1, G00-G02, G04.0, G04.2, G05-G09, G53.1, G63.0, G73.4, G93.7, G94.0, H00, H01.0, H03, H05.0, H06.1, H10.0, H10.2-H10.5, H10.8 -H10.9, H13.0-H13.2, H19.0-H19.2, H22.0, H32.0, H44.0, H60, H62.0-H62.4, H66, H67.0-H67.1, H70.0, H75.0, H83.0, H92.1, H94.0, I00-I02, I30.1, I32.0-I32.1, I33.0, I39, I40.0, I41.0-I41.2, I43.0, I52.0- I52.1, I68.1, I79, I98.0-I98.2, I98.8, J00-J06, J09-J22, J31-J32, J34.0, J35.0, J36-J37, J39.0-J39.1, J40, J41.1, J44.0, J47, J65, J85-J86, K04.6-K04.7, K11.3, K12.2, K23.0, K35-K37, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.9, K67, K75.0, K77.0, K81, L00-L08, L30.3, L70.2,M00-M01, M03, M46.2-M46.5, M49.0-M49.3, M60.0, M63.0-M63.2, M65.0-M65.1, M68.0, M71.0-M71.1, M86, M90.0-M90.2, N08.0, N10, N11.0-N11.1, N11.8, N12, N13.6, N15.1, N16.0, N29.0-N29.1, N30.0-N30.3, N33-N34, N35.1, N39.0, N41, N43.1, N45, N48.1-N48.2, N49, N51, N61, N70-N74, N75.1, N76.0-N76.4, N77.0-N77.1, N98.0, O03.0, O03.5, O04.0, O04.5, O05.5, O08.0, O23, O85, O86, O91, O05.0, O98, R00, R01, R02, R50.8, R50.9, R57.2, T79.3, T80.2, T81.4, T82.6, T82.7, T83.5-T83.6, T84.5-T84.7, T85.7, T87.4, T88.0
Abdominal	001-003.0, 003.8-006.3, 007-009, 014, 032.83, 039.2, 070, 098.86, 112.85, 540-542, 569.5, 572-572.1, 573.1-573.3	A00-A02.0, A02.8, A02.9, A03-A06.4, A07-A09, A18.3, A42.1, B15-B19, B37.8, K35-K37, K57.0, K57.2, K57.4, K57.8, K63.0, K67.1, K75.0, K77.0
Dialysis-related	567, 996.62, 996.68	T82.7, K65.0, K65.9
Genitourinary	016, 032.84, 054.1, 098.0–098.3, 112.1–112.2, 590, 595.0–595.4, 597, 598.0, 599.0, 601, 603,1, 604, 607.1–607.2, 608.0, 608.4, 614–616.1, 616.3–616.4, 616.8, 996.64	A18.1, A60.0, A54.0-A54.2, B37.3-B37.4, N10, N11.0-N11.1, N11.8, N12, N30.0-N30.3, N33, N34, N35.1, N39.0, N41, N43.1, N45, N48.1-N48.2, N49, N51, N70-N74, N75.1, N76.0-N76.4, N77.0-N77.1, T83.5-T83.6
Musculoskeletal	015, 098.5, 711, 727.89, 728.0, 730-730.3, 730.8-730.9, 996.66-996.67	A18.0, A54.4, M00-M01, M03, M46.2-M46.5, M49.0-M49.3, M60.0, M63.0-M63.2, M65.0-M65.1, M68.0, M71.0-M71.1, T84.5-T84.7
Other prosthetic devices	996.69	T85.7
Pneumonia	480-486, 487.0,	J12-J18, J10.0, J11.0, J85.1

Septicemia	003.1, 022.3, 036.2, 038, 054.5, 112.5, 790.7, 785.52	A40 -A41, O85, A02.1, A22.7, A26.7, A32.7, A39.2, A39.3-A39.4, A42.7, B37.7, R57.2
Skin	006.6, 017.0, 031.1, 032.85, 039.0, 054.0, 103, 110–111, 112.3, 116.2, 680–686.9, 706.0	A06.7, A18.4, A31.1, A36.3, A43.1, A44.1, A67, B00.0, B00.1, B35, B36, B37.2, B38.3, B40.3, B43.0, B45.2, B46.3, B48.0, L00-L08, L30.3, L70.2
Other	All infection codes not included in abdominal, dialysis-related, genitourinary, musculoskeletal, pneumonia, septicemia or skin	All infection codes not included in abdominal, dialysis-related, genitourinary, musculoskeletal, pneumonia, septicemia or skin.

Table 15. Codes used to determine IRH