BIOCOMPATIBLE PERITONEAL DIALYSIS (PD) SOLUTION

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BIOCOMPATIBLE PERITONEAL DIALYSIS (PD) SOLUTION

EXECUTIVE SUMMARY

Background

End stage renal disease (ESRD) is defined as irreversible decline in kidney function, which is severe enough to be fatal in the absence of dialysis or transplantation. According to Global Burden of Disease study, in 2015 1.2 million people died from kidney failure; an increase of 32% since 2005. In 2010, an estimated 2.3 - 7.1 million people with end-stage kidney disease died without access to dialysis. In Malaysia, a population-based study in 2011 reported that 9.1% of Malaysians were found to have chronic kidney dialysis (CKD). Breakdown of the prevalence by stages were as follows; stage 1, 4.16%; stage 2, 2.0%; stage 3, 2.26%; stage 4, 0.24%; and stage 5, 0.36%.

In 2016, the most common type of renal replacement therapy (RRT) in Malaysia was haemodialysis (HD) with the prevalence of 1,059 patients per million population (pmp) followed by peritoneal dialysis (PD) (127 patients pmp) and renal transplantation (RT) (59 patients pmp). Between 2007 and 2016, the prevalence of HD and PD in Malaysia increased 2.3 times and 2.5 times, respectively. The annual death rate of patients on dialysis in 2015 was 13.4% which the annual death rate among PD patients was 16.9% and 13% among HD patients.

Peritoneal dialysis is a home based therapy which a patient is required to perform three to four PD exchanges per day. The PD solution or dialysate play crucial role in dialysis. The dialysate solution is a nonsterile aqueous electrolyte solution that is similar to the normal levels of electrolytes found in extracellular fluid with the exception of the buffer bicarbonate and potassium. Dialysate solution is almost an isotonic solution, with the usual osmolality of approximately 300 ± 20 miliosmoles per liter (mOsm/L). The PD solutions can be divided into conventional PD solutions and novel solutions with more biocompatible characteristics (such as neutral-pH, low glucose degradation products - GDPs solutions including icodextrin). Conventional PD solutions are characterized by several undesirable characteristics which result in adverse clinical outcomes.

Thus, there was a request from the National Advisor of Nephrologist to look at the potential of expanding PD using biocompatible PD solution for sake of the patient's safety as well as cost-saving compared to conventional PD solution. The nephrologist also hoping to develop a Clinical Practice Guideline (CPG) and standard operating procedure (SOP) in Malaysia for physicians, nephrologist and PD nurses on the advantage, indications and prescriptions of biocompatible PD solution.

Objective/aim

To assess the efficacy or effectiveness, safety, and cost-effectiveness of biocompatible PD solution

Results & Conclusion

A total of 678 titles were screened and after removing duplications and irrelevant titles, 151 abstracts were screened. Out of 151 abstracts, 132 studies that did not meet the inclusion criteria or already included in the selected SR were excluded. Nineteen full texts studies were assessed for eligibility. Out of 19 studies, nine studies were included in the report; all nine studies were on the effectiveness and safety. No economic evaluation studies retrieved specifically on biocompatible PD solution.

The included studies consisted of three systematic reviews (SR) with meta-analysis (MA), two RCT, and four cohort studies. Those studies were conducted in Taiwan, Hong Kong, Canada, South Korea, UK, Serbia and Japan. The study populations were among ESRD patients from all over the world including European country, Spain, New Zealand, Brazil, USA and Asia.

Efficacy and Effectiveness

Based on the review, the evidence showed that neutral pH, low GDP PD solution was better compared to conventional PD solution in improving the residual renal function (RRF) or urine volume. However, for Icodextrin, the RRF showed no significant difference compared to conventional PD solution in SR and MA but a little increase and better improvement in another studies after six months. Another main outcome was on cardiovascular events, the Icodextrin solution showed an improvement in coronary heart failure (CHF). The cumulative incident CHF was lower in Icodextrin users than non-users. Besides, the CHF incidence rate also greater in diabetic patient without using Icodextrin subgroups than in diabetic patient who were using Icodextrin PD solution. The hazard ratio of CHF in diabetes patient on Icodextrin also lower compared to diabetes patient without Icodextrin PD solution. On the other hand, Icodextrin showed no significant difference in any changes in cardiovascular structure and function, however, this finding requires further study.

On the other hand, for other outcomes the evidence varied and most of the findings was at low certainty evidence. The biocompatible or neutral pH, low GDP PD solution showed lower peritoneal ultrafiltration compared to conventional PD solution after four hours of PD, minimal changes in peritoneal membrane and MIA syndrome (chronic inflammation, malnutrition and atherosclerosis). However, for Icodextrin, the included study showed there was an increase trend but not significant in ultrafiltration capacity. There was also no significant difference in peritoneal small solute clearance, peritonitis rate and patient survival between biocompatible or neutral pH, low GDP PD solution and Icodextrin. Meanwhile, findings for inflow pain and hospitalisation was uncertain in all biocompatible PD solutions.

Organisational Issue

The above review showed that there was no difference to death-censored technique failure between neutral pH, low GDP PD solution and conventional PD solution. Meanwhile for Icodextrin, the technique failure was uncertain except one study showed that non-compliance in Icodextrin group was significantly lower that non-Icodextrin group.

Safety

Safety issue for both neutral pH, low GDP and Icodextrin PD solution was uncertain.

Cost

No economic evaluation comparing biocompatible PD solution and conventional PD solution retrieved. The economic evaluation papers retrieved showed that peritoneal dialysis was cost saving over haemodialysis.

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Methods

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 2nd March 2020. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

Study was limited to 2000 onwards. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

BIOCOMPATIBLE PERITONEAL DIALYSIS (PD) SOLUTION

1. BACKGROUND

End stage renal disease (ESRD) is defined as irreversible decline in kidney function, which is severe enough to be fatal in the absence of dialysis or transplantation. The ESRD is included under stage 5 of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease (CKD) with an estimated glomerular filtration rate (GFR) less than 15mL per minute per 1.73m^2 body surface area, or those requiring dialysis irrespective of GFR. Reduction in or absence of kidney function leads to a host of maladaptive changes including fluid retention (extracellular volume overload), anaemia, disturbances of bone and mineral metabolism, dyslipidaemia, and protein energy malnutrition.[1]

According to Global Burden of Disease study, in 2015 1.2 million people died from kidney failure; an increase of 32% since 2005. In 2010, an estimated 2.3 - 7.1 million people with end-stage kidney disease died without access to dialysis.[2] In Malaysia, a population-based study in 2011 reported that 9.1% of Malaysians were found to have CKD. The global prevalence of CKD is between 11% and 13%.[2] Breakdown of the prevalence by stages were as follows; stage 1, 4.16%; stage 2, 2.0%; stage 3, 2.26%; stage 4, 0.24%; and stage 5, 0.36%.[3]

In 2015, the equivalent incidence and prevalence of patients on dialysis were 249 and 1,220 per million populations, respectively. Among the incident dialysis patients, 15.4% were on PD while only 10% of the prevalent dialysis patients were on PD. The annual death rate of patients on dialysis in 2015 was 13.4% which the annual death rate among PD patients was 16.9% and 13% among HD patients. The difference in annual death rate between the two modalities persisted over the last two decades and was partly contributed by the negative selection of patients for peritoneal dialysis and the changing of modality from HD to PD due to severe cardiovascular disease.[5] In 2016, the most common type of renal replacement therapy (RRT) in Malaysia was haemodialysis (HD) with the prevalence of 1,059 patients per million population (pmp) followed by peritoneal dialysis (PD) (127 patients pmp) and renal transplantation (RT) (59 patients pmp). Between 2007 and 2016, the prevalence of HD and PD in Malaysia increased by 2.3 times and 2.5 times, respectively.[3] Only 1% of the total dialysis patients received treatment at home or office.[4]

Peritoneal dialysis is a home based therapy which a patient is required to perform three to four PD exchanges per day. The PD solution or dialysate play crucial role in dialysis. The dialysate solution is a nonsterile aqueous electrolyte solution that is similar to the normal levels of electrolytes found in an extracellular fluid with the exception of the buffer bicarbonate and potassium. Dialysate solution is almost an isotonic solution, with the usual osmolality of approximately 300 ± 20 miliosmoles per liter (mOsm/L).[6] The PD solutions can be divided into conventional PD solutions and novel solutions with more biocompatible characteristics (such as neutral-pH, low glucose degradation products-GDPs solutions). Conventional PD solutions are characterized by several undesirable characteristics which result in adverse clinical outcomes. Consequently, there has been a great interest in manufacturing newer solutions with more

'biocompatible' features to mitigate these adverse effects. This has led to the development of neutral-pH, low or ultralow GDP solutions, glucose-sparing PD solutions (Icodextrin and amino acid solutions), solutions using alternative osmotic agents (such as hyperbranched polyglycerol) and low-sodium PD solutions.[7]

Thus, a request was received from the National Advisor of Nephrology Services to evaluate the potential in expanding PD using biocompatible PD solution in order to improve patient's safety as well as a more cost-saving measure compared to conventional PD solution. The findings will also be incorporated in the Clinical Practice Guidelines (CPG) and standard operating procedure) SOP in Malaysia.

2. OBJECTIVE/AIM

To assess the efficacy or effectiveness, safety and cost-effectiveness of biocompatible PD solution

3. TECHNICAL FEATURES

3.1 Peritoneal Solution

Peritoneal dialysis is a life-saving, renal replacement therapy (RRT) for CKD stage 5 dialysis (CKD5D). Its use is increasing worldwide.[4] During PD, peritoneal solution or also known as cleaning fluid flows through a tube into parts of the abdomen. The lining of the abdomen called the "peritoneal membrane" act as a filter, to remove toxins and fluids from the body. The used of PD can be limited by peritoneal membrane injury, which is partly a result of biologically 'unfriendly' PD solutions, which are acidic and consist of high levels of glucose and toxic glucose breakdown products (conventional PD solution). To overcome these hurdles, biocompatible PD solutions (i.e with a neutral pH and low levels of glucose breakdown products or with a glucose-alternative like Icodextrin) have been manufactured with the aim of providing patient benefit.[8]

The PD solution is divided into two types:[4]

i) Conventional PD solution

Conventional PD solutions have an acidic pH and rely on hyperosmolar dextrose solutions to achieve an adequate gradient for ultrafiltration (UF) across the peritoneal membrane. The low pH and hyperosmolarity have been implicated in acute toxicity, such as inflow pain.[8] Conventional PD solution are characterised by several undesirable characteristics, including acidic pH (5.2-5.5), high glucose concentrations (13.6-42.5g/L), hyperosmolarity (360.511mOsm/kg) and relatively high concentrations of glucose degradation products (GDPs). These characteristics can cause adverse clinical outcomes, including acute peritoneal membrane toxicity (manifested as inflow pain), chronic peritoneal toxicity (including membrane failure, ultrafiltration failure, peritonitis and encapsulating peritoneal sclerosis) and adverse systematic sequel (including hyperglycaemia, dyslipidaemia, metabolic syndrome, cardiovascular disease and residual renal function decline).[7]

ii) Biocompatible PD solution

Biocompatible, dialysis solutions have been design to minimize perturbation of the physiological environment in the peritoneal cavity. The main approaches to create biocompatible solutions is to generate solutions with a neutral pH and low GDP content, use of bicarbonate (± lactate) buffer, substitution of dextrose with glucose polymers (resulting in low GDP content although with an acidic pH), and use of amino acids as the osmotic agent. The biocompatible PD solution is belief to cause less damage to the peritoneal membrane than conventional fluids, and hence improve patient outcomes.[8]

Types of Biocompatible PD solutions:

a) Neutral pH, low GDP
In neutral pH, low GDP, glucose is separated from other electrolytes in one or more chambers and sterilised at a very low pH (2.58 - 4.2) to minimise the productions of GDPs. The remaining solution is kept at an alkaline pH (8.0 - 8.6) in the other compartment. When the PD solution need to be used, the contents of the two compartments are allowed to mix by breaking a lambda seal or frangible pin, resulting in the infusion of neutral pH (6.8 - 7.3), and either a low GDP content or an ultralow GDP content (less than 80 µmol/L) PD solution into the peritoneal cavity.[7]

b) Glucose polymer (Icodextrin)
Icodextrin is a starch-derived, iso-osmolar, high molecular weight glucose polymer PD solution. The structure of Icodextrin is similar to glycogen. The pharmacokinetics of Icodextrin in blood following intra-peritoneal administration imitates a simple, single-compartment that can be approximated by zero-order absorption and first-order elimination. Icodextrin is slowly absorbed via the lymphatics and let the osmotic gradient dissipates slowly as compared to glucose, which is absorbed via the small pores of the peritoneal membrane. This provides much greater net ultrafiltration during the long dwell, especially in patient with higher transporter status.[7]

c) Amino acid solutions
Peritoneal dialysis causes loss of protein and amino acids in the dialysate, which contributes to the development of protein and energy malnutrition in these patients. Amino acid solutions were developed with an aim to compensate for protein loss. The amino acid PD solutions are osmotically equivalent to 1.5% glucose PD solution, its use is limited to a single daily exchange due to risk of worsening systemic acidosis and uraemia.[7]

d) Combination regimens
Combination of Icodextrin, amino acid and neutral pH, low GDP solution as part of glucose-sparing PD therapy.[7]

3.2 Main Outcome of Peritoneal Dialysis

Based on study by Maruyama Y et al.[8] and Xue J et al.[9], the important outcomes monitored during PD and HD were incidence of infection peritonitis, cardiovascular events, major morbidity events, survival time and survival rate, RRF and quality of life.

Both studies also reported that among diabetic patient, high mortality rate was observed among diabetic patient than non-diabetic. However, mortality rate among diabetic patient with PD was higher than HD.[8-9]

4. METHODS

4.1. Searching

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 2 March 2020. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

Study was limited to 2011 onwards. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles.

Appendix 1 showed details of the search strategies.

4.2. Selection

One reviewer screened the titles and abstracts against the inclusion and exclusion criteria and reviewed by senior reviewer.

The inclusion and exclusion criteria were:

Table 1: Inclusion Criteria

Inclusion criteria	
Population	Peritoneal dialysis
Interventions	Biocompatible PD solution (Icodextrin 7.5% (ICO) and low-glucose degradation product (GDP)
Comparators	Conventional PD solution
Outcomes	Effectiveness such as residual renal function (RRF)/ urine volume, peritoneal ultrafiltration capacity, peritoneal solute transport rate, peritoneal small solute clearance, peritonitis, inflow pain, organisational, safety and cost-effectiveness
Study design	Systematic review (SR), meta-analysis (MA), randomised controlled trial (RCT), and cohort study

Table 2: Exclusion Criteria

Exclusion criteria	
Study design	Animal studies, laboratory studies, case reports, case series
Intervention	Other than biocompatible PD solution
Outcome	Non-medical condition such as wellness, dermatology
	Non-English full text article

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP), Cochrane tools, and evidence graded according to the US / Canadian Preventive Services Task Force (Appendix 2). Data were extracted from included studies using a pre-designed data extraction from (evidence table as shown in Appendix 3) and presented in tabulated format with narrative summaries. Meta-analysis was not conducted for this technology review; however, one current meta-analysis was conducted by Cochrane Review in 2018.

5. RESULTS AND DISCUSSION

A total of 678 titles were screened and after removing duplications and irrelevant titles, 151 abstracts were screened. Out of 151 abstracts, 132 studies that did not meet the inclusion criteria or already included in the selected SR were excluded. Nineteen full texts studies were assessed for eligibility. Out of 19 studies, nine studies were included in the report; all nine studies were on the effectiveness and safety. No economic evaluation studies retrieved specifically on biocompatible PD solution.

The included studies consisted of three systematic reviews (SR) with meta-analysis (MA), two RCT, and four cohort studies. Those studies were conducted in Taiwan, Hong Kong, Canada, South Korea, UK, Serbia and Japan. The study populations were among ESRD patients from all over the world including European country, Spain, New Zealand, Brazil, USA and Asia. The characteristics of included studies were discussed in the next section. Figure 1 shows the flow chart of the study selection.

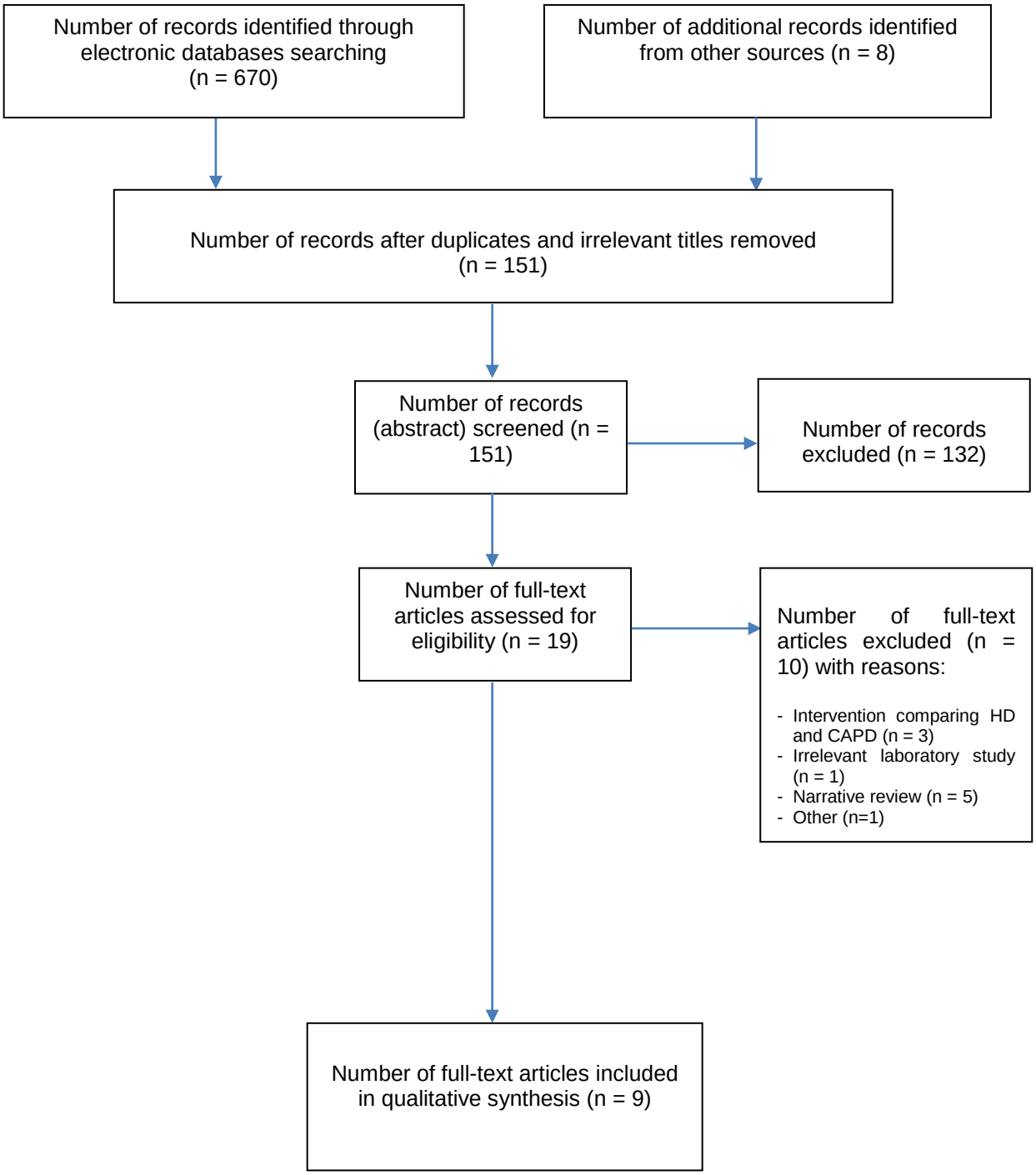

Figure 1: Flow chart of study selection

5.1 CRITICAL APPRAISAL OF INCLUDED STUDIES

Risk of bias of an RCT was assessed by Cochrane Risk of Bias Tool. Whereas for SR and other studies, criteria for assessment was developed based on CASP checklist. The risk of bias was evaluated by answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

The assessment of risk of bias revealed that fair quality of evidence for two RCTs as the allocation concealment and blinding was not discussed. Other studies have small sample numbers and issues on confounding factors.

The results of risk of bias of included studies are summarised in Figure 2 to Figure 4.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?	
Kanno T. (2020)	+	+	+	+	
Goossen K. (2019)	+	+	+	+	
Htay H. et al (2018)	+	+	+	+	+

Figure 2. Critical appraisal for Systematic Review (CASP checklist)

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Chen JB. et al. 2018	+	?	?	+	+	+
Sikaneta T. et al 2016	+	?	+	+	+	+

Figure 3: Assessment of risk of bias of RCT (Cochrane's tool)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Han SH et al. 2012	+	+	+	+	+
Tawada M. et al. 2018	+	+	+	?	+
Stankovic-Popovic A et al. 2011	+	+	+	?	+
Wang IK et al. 2018	+	+	+	+	+

Figure 4: Critical Appraisal for cohort (CASP checklist)

5.2. EFFICACY/ EFFECTIVENESS

5.2.1 Residual Renal Function (RRF)/ Urine Volume

a) Neutral pH, Low GDP versus Conventional Glucose PD

Htay H et al. conducted SR and MA to look at the benefits and harms of the biocompatible PD solutions compared to conventional PD solutions. The SR included 42 eligible studies (1997 - 2016) which involved 3,262 adults and children. Out of 42 studies, 29 studies compared neutral pH, low GDP PD solution with conventional PD solution. The studies monitored the RRF at three different durations; up to 12 months, 12 to 24 months and more than 24 months. Overall, the SR and MA showed that there was high certainty evidence of neutral pH and low GDP PD solution improved the preservation of RRF compared to standard PD solution [Standard mean difference (SMD): 0.19; 95% CI: 0.05,0.33; I^2 = 0%]. This result was approximated to mean difference (MD) in glomerular filtration (GFR) of 0.54ml/min/1.73m^2 (95% CI 0.14, 0.93). The individual RRF effects for different duration were shown in Table 3. [10, level 1]

Table 3: Residual Renal Function of Biocompatible PD Solution versus Conventional PD Solution

Duration	Studies / Participants	Standard Mean Difference (SMD)	Mean Difference in GFR
Up to 12 months	11 studies / 722 participants	SMD 0.18, (95% CI: 0.05 to 0.32; I^2 = 3%)	MD in GFR of 0.59 mL/min/1.73 m^2 (95% CI: 0.16 to 1.05)
12 to 24 months	10 studies / 641 participants	SMD 0.25, (95% CI: 0.10 to 0.41; I^2 = 0%)	MD in GFR of 0.71 mL/min/1.73 m^2 (95% CI: 0.28 to 1.16)
more than 24 months	6 studies / 343 participants	SMD 0.30, (95% CI: 0.08 to 0.51; I^2 = 0%)	MD in GFR of 0.85 mL/min/1.73 m^2 (95% CI: 0.23 to 1.44)

They also showed higher urine volume with neutral pH, low GDP solution as compared with conventional glucose PD solution [MD 114.37 ml/d (95% CI: 47.09, 181.65; I^2 = 3%)]. The included studies for this outcome were 11 with 791 participants. However, there was no difference in urine volume up to 12 months' follow-up. The benefit was observed after 12 months' follow-up as shown in Table 4. [10, level 1]

Table 4: Urine Volumes at Difference Duration (Daily Residual Diuresis)

Duration	Studies / Participants	Mean Difference
Up to 12 months	10 studies / 819 participant	MD 69.72 mL/d, 95% CI -55.95 to 195.40; I^2 = 60%
12 to 24 months	8 studies / 579 participants	MD 110.57 mL/d, 95% CI 40.81 to 180.34; I^2 = 0%
more than 24 months	3 studies / 279 participants	MD 169.22 mL/d, 95% CI 23.98 to 314.46; I^2 = 0%

Sikaneta T et al. conducted an RCT to examine the effect of biocompatible PD solution (low GDP PD solution) over conventional PD solution. The subjects were recruited from pre-dialysis outpatient clinics at The Scarborough Hospital in Ontario, Canada and Princess Margaret in Hong Kong. These subjects were randomised into an open-label parallel group trial to receive Gambrosol; Trio (biocompatible PD solution) or Dianel (conventional PD solution). At the beginning, there were 51 subjects in low GDP group and 50 in the conventional group. However, after two years of completed follow-up, there were 36 subjects left in low GDP PD solution and 31 subjects in conventional group. The follow-up was completed within two years. The RRF declined by 0.132 ml/min/1.73m^2/month in low GDP group and 0.174 ml/min/1.73m^2/month in conventional group; p = 0.001.[11, level 1]

They also reported that urine volume declined by 30ml/month in biocompatible PD solution group and 39ml/month in conventional PD solution group; p = 0.003. Oliguria was reported less frequently in biocompatible PD solution group; p = 0.001.[11, level 1]

b) Glucose Polymer (Icodextrin) versus Glucose PD Solution

Kanno A et al. conducted an SR and MA to determine the risks and benefits of icodextrin compared with a glucose-based solution with respect to clinically important and patient-centred outcome. The authors included RCTs that compared icodextrin with glucose solutions among patients on PD. There were 13 studies included with a total of 1,275 patients. For residual renal function, which was determined from glomerular filtration rates or renal creatinine clearance, the study showed that there was no significant difference between icodextrin and glucose PD solution; MD 0.56mL/min; 95% CI -0.37 to 1.49; p = 0.24, I^2 = 0 with moderate certainty evidence of five RCTs of 181 patients. For urine volume, the authors reported that icodextrin was not associated with urine volume; MD 106.08mL/day; 95% CI -173.29, 385.45; p = 0.13; I^2 = 39%, with low certainty evidence of four RCTs of 136 patients. However, one RCT demonstrated that icodextrin was associated with significant higher daily urine volumes than glucose dialysate at 12 months. The authors also reported that the icodextrin significantly decreased the frequency of reported episodic uncontrolled peritoneal fluid overload in four RCTs of 236 patients (RR 0.31; 95% CI 0.12, 0.82; p = 0.02, I^2 = 0%; moderated certainty evidence).[21, level 1]

The SR and MA by Htay H et al. compared Icodextrin and conventional glucose PD solution. In the low certainty evidence, the Icodextrin may make little or no difference to RRF. The included studies were four with total of 114 participants. The decline rate was low in icodextrin groups regardless of initial RRF or starting PD modality. The SMD was 0.12 (95% CI: -0.26, 0.49, p= 0.5; I^2 = 0%) which was approximated to a mean difference in renal CrCl of 0.30 mL/min (95% CI: - 0.65, 1.23). The authors also reported that in 3 studies with 69 patients (low certainty evidence), icodextrin make little or no difference in

the daily urine volumes; MD -88.88mL/d, (95% CI: -356.88,179.12, p= 0.5; I^2 = 0%). However, there was one study reported that six months used of Icodextrin had better maintenance of urine volume when compared to 2.27% dextrose PD solution.[10, level 1]

5.2.2 Peritoneal Ultrafiltration (UF) Capacity

a) Neutral pH, Low GDP versus Conventional Glucose PD

The pooled analysis included nine studies with 414 participants reported by Htay H et al. (low certainty evidence) showed the four hours peritoneal UF measured during a peritoneal equilibrium test may be lower in the neutral pH, low GDP solution; SMD -0.42 (95% CI: -0.74, -0.10; I^2 = 51%); the estimated MD -69.72 mL/4 hours, (95% CI: -122.84, -16.60), minimal changes in peritoneal membrane and MIA syndrome (chronic inflammation, malnutrition and atherosclerosis).[10, level 1]

b) Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution

Current SR with MA by Kanno A. et al. reported that icodextrin solution did not lead to a significant increase in UF compared with glucose solutions. The findings were reported in six RCTs of 252 patients; MD 186.76mL/day; 95% CI -47.08, 420.59; p = 0.12, I^2 = 64%; low certainty evidence.[21, level 1]

The SR with MA by Goossen K. et al. compared once-daily long-dwell icodextrin to glucose-only PD among patients with kidney failure undergoing PD. The included studies were 20 and only one study was excluded from meta-analysis. The other 19 studies which were included in the meta-analysis consisted a total of 1,685 patients. The primary outcomes were patient survival (number of deaths during treatment), PD technique survival (number of conversions to HD), health related quality of life (HRQoL) and peritoneal ultrafiltration. Meanwhile the secondary outcomes were mainly on safety including adverse events and peritonitis incidence. For peritoneal ultrafiltration the authors reported that icodextrin was more effective than glucose group for up to 6 months (medium-term (MD) 208.92 [95% CI 99.69-318.14mL/24h] with high certainty of evidence), but no difference between groups was seen in the long-term.[20, level 1]

The Htay H. et al. also previously reported that the Icodextrin was uniformly improved peritoneal UF compared with glucose exchanges; MD 448.54 mL/24h, (95% CI: 289.28, 607.80; I^2 = 0%).[10, level 1]

5.2.3 Peritoneal Solute Transport Rate

a) Neutral pH, Low GDP versus Conventional Glucose PD Solution

According to SR and MA by Htay H et al., at four hours' dialysate-to-plasma creatinine ratio (D/P_{Creat}) measured during a peritoneal equilibrium test may be higher in the neutral pH, low GDP solution group; MD 0.01 (95% CI: 0.00, 0.03; I^2 = 1%), with low certainty evidence (10 studies, 746 participants). However, subgroup analysis with patient characteristics fluid types and study design showed no significant difference in 4 hrs D/P_{Creat} values between the neutral pH, low GDP solution and control groups.[10, level 1]

b) Glucose Polymer (Icodextrin) versus Glucose PD Solution

Kanno A. et al. adopted dialysate-to-plasma creatinine ratio (D/P Cr) as a marker of peritoneal function. However, they found that the amount of clinical research was insufficient to evaluate outcomes and icodextrin did not affect the D/P Cr with a moderate level of heterogeneity in two RCTs that included 105 patients (MD 0.001; 95% CI -0.07, 0.07; p = 0.97, I^2 = 65%; very low certainty evidence.) [21, level 1]

5.2.4 Peritoneal Small Solute Clearance

a) Neutral pH, Low GDP versus Conventional Glucose PD

The SR and MA by Htay H et al. stated that neutral pH low GDP PD solution may make little or no difference to peritoneal creatinine clearance; MD -0.44 L/week/1.73m^2, (95%, CI: -2.03, 1.15; I^2 = 0%) or in peritoneal urea clearance; MD -0.01, (95%, CI: -0.12, 0.09; I^2 = 26%). The analysis included seven studies with total of 510 participants for creatinine clearance and six studies for urea clearance participants (n = 422).[10, level 1]

b) Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution

In low certainty evidence (three studies with total of 237 participants), Htay H et al. reported that Icodextrin may make little or no difference to peritoneal CrCl; SMD 0.36, (95% CI: 0.24, 0.96; I^2 = 66%); with estimated MD 0.36 mL/min (95% CI: 0.24, 0.95).[10, level 1]

5.2.5 Inflow Pain

a) Neutral pH, Low GDP versus Conventional Glucose PD

Htay H et al. reported that in very low certainty evidence (one study, 58 participants), it is uncertain whether neutral pH, low GDP solution use led to any differences and may decrease the incidence of inflow pain; RR 0.51, (95% CI: 0.24, 1.08).[10, level 1]

5.2.6 Patient Survival

a) Neutral pH, Low GDP versus Conventional Glucose PD

Neutral pH, low GDP solution also may make little or no difference to death; RR 0.73, (95% CI: 0.47, 1.14; I^2 =0%), in low certainty evidence (15 studies, n = 1,229).[10, level 1]

b) Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution

Kanno A. et al. reported that the effects of icodextrin and glucose solutions on patient survival did not significantly differ in 10 RCTs of 1,106 patients (RR 0.75; 95%CI 0.33, 1.71; p = 0.49, I^2 = 0%). However, the point estimate was better for icodextrin than glucose solutions by seven patients' reductions among 1000 patients.[21, level 1]

Goossen K. et al. reported in the SR with MA, icodextrin probably decreased mortality risk compared to glucose PD solution (Peto OR, 0.49 [95% CI 0.24, 1.00) and for causes of death with moderate heterogeneity.[20, level 1]

On the other hand, Htay H et al reported that in the context of low event numbers and short follow-up durations (six studies with 816 participants), it was uncertain whether Icodextrin improve patient survival; RR 0.82, (95% CI: 0.32, 2.13; I^2 = 0%.[10, level 1]

Han SH et al. conducted a post-hoc analysis of retrospective cohort to investigate whether Icodextrin solution may confer patient and technique survival advantages in PD patients. The authors conducted the post-hoc analysis using Baxter Korea database of Baxter Healthcare Corporation. A total of 2,163 ESRD patients included in the study used either biocompatible PD solution (Physionel) or conventional PD solution (Dianel) supplied by Baxter. The mean follow-up duration of PD was 23.7 ± 12.4 months with a range of 3.1 – 50.3 months. Out of 2,163 patients, 641 met the criterion for the Icodextrin group and the other 1,522 were categorized as non-Icodextrin group. In non-Icodextrin group, 907 (59.6%) patients never used Icodextrin solution and remaining 615 patients used Icodextrin at least one day. Compared with non-Icodextrin group, more patients with diabetes (63.7% versus 48.7%, p < 0.001), low SES (32.3% versus 23.4%, p < 0.01) and used of B/L solution (32.1% versus 22.1%, p <0.001) in the Icodextrin group. The unbalance condition at baseline between both groups were controlled by using propensity score (PS) matching. After the PS matching, 74 patients (5.8%) treated with automated PD (APD), which was 45 patients (7.0%) in the Icodextrin groups and 29 patients (4.5%) in the non-Icodextrin group but, the difference was not statistically significant. In the matched cohort, all-cause deaths occurred in 92 (11.4%) patients in the Icodextrin group compared with 128 (20.0%) in the non-Icodextrin group (p = 0.006). Within two and four years, patient's mortality rates were 14.2% and 26.4% in the Icodextrin group and 20.0% (p = 0.004) and 31.1% (p = 0.004) in non-Icodextrin group). Based on multivariate Cox analysis; adjusted age, gender, diabetes, cardiovascular comorbidity, types of PD solution, the Icodextrin used was associated with significantly lower risk of death (HR 0.69; 95% CI 0.53, 0.90; p = 0.006). The authors conducted sensitivity analysis on 804 patients (381 patients in Icodextrin group and 423 patients in non-Icodextrin group), there was no significant difference in residual urine output at initiation of PD between the two matched groups (608.5 ± 418.4 ml/day in Icodextrin group versus 612.3 ± 414.9 ml/day in non-Icodextrin group, p = 0.898. After adjustment of residual urine output, survival benefit of Icodextrin remained significant (HR = 0.63; (95% CI: 0.45, 0.90; p = 0.011). The causes of death in each group showed no difference; either in cardiovascular death, infectious death, advanced liver disease, malignancy, malnutrition or other causes which not mentioned.[12, level II-2]

5.2.7 Effects of Icodextrin on Cardiovascular (CHF and cardiac structure)

Chen JB et al. conducted an RCT to evaluate the longitudinal changes in cardiac structure and function in APD patients using either Icodextrin solution or glucose-based (GLU) solution. Studies was started in June 2005 and completed in May 2015. Patients were selected from PD unit in Kaohsiung Chang Gung Memorial Hospital, Taiwan and were randomised into two groups (21 patients in Icodextrin group and 22 patients in GLU group). The cardiac structure and function were examined with echocardiography at baseline and subsequently in one-year intervals. Patients were requested to visit the PD outpatient clinic at least once every month and by telephone at least once a week. In Icodextrin group, participants received long-dwell exchange for 10 to 12 hours with 7.5% Icodextrin PD solution in daytime and in GLU group, participants received one or two exchanges with glucose-based PD solution in daytime. Out of 43 participants, 38 completed the study (20 in Icodextrin group and 18 in GLU group). Diabetic nephropathy more prevalent in Icodextrin group. The analysis on cardiac showed that compared with

Icodextrin group, the GLU group had significantly lower baseline of left ventricular end-systolic dimension (LVESD); 35.00mm versus 30.49mm and lower baseline left ventricular end-systolic volume (LVSEV); 53.48mm^3 versus 39.00mm^3. Meanwhile, for changes in cardiac measurements from baseline to 24 months, in Icodextrin group, the LAD was significantly increased but LVEDV, LVSEV, and IVS was significantly decreased. In LV septal diastolic function measurement, only septal EMV showed significant increased from baseline to 24 months (5.43 to 5.51m/s). Then for GLU group, all LAD, LVED, LVESD, LVEDV and LVESD were significantly increased. Then in LV systolic function measurement, only LVEF had significant increased. However, there was significant decreased in peak end-diastolic volume (EDV) (70.67 to 68.25m/s) from baseline to 24 months. The authors concluded that there were no major differences in cardiac structure and function in both Icodextrin and GLU PD solution in incidence-APD thus further research with bigger samples size is required.[13, level 1]

Wang IK et al. conducted prospective cohort study to investigate whether Icodextrin treatment could reduce the risk of congestive heart failure (CHF) in PD patients. The study compared risks of new-onset CHF between PD patients with and without Icodextrin treatment. A total of 5,462 newly diagnosed patients with end stage renal disease (ESRD) who underwent PD treatment more than 90 days were involved in the study. They were 2,931 Icodextrin users and 2,531 non-Icodextrin users. All the patients were follow-up from index date (date of PD initiation) until the date when CHF were diagnosed or until renal transplantation, death, withdrawal from the insurance or at the end of the follow-up. Along the study period, a total of 735 (25.1%) patients with Icodextrin treatment and 519 (20.5%) patients without Icodextrin treatment switched to haemodialysis (HD). The study found that, proportional cumulative incident CHF was lower in Icodextrin users than in non-users after mean follow-up periods of 3.06 ± 1.65 years and 2.64 ± 1.70 years respectively. After controlling all covariates: the incidence rate of CHF was 26% lower in Icodextrin users than in non-users (13.7%; [95% CI: 12.4, 15.1] vs 18.6; [95% CI: 16.6, 20.9] per 1000 person-years), the users had an adjusted HR of 0.67 (95% CI: 0.52, 0.87), compared with non-users. The authors also demonstrated the CHF risk by diabetes status for both groups and the study showed that the incidence rates of CHF were greater in diabetic subgroups than in non-diabetic subgroups. The highest CHF rate was 28.5 (95% CI: 22.8, 35.4) per 1000 person-years in Icodextrin non-users with diabetes but in Icodextrin users with diabetes, the rate was reduced to 17.8 (95% CI: 15.3, 20.7) per 1000 person-years or to 11.0% (95% CI: 9.56,12.7) per 1000 person-years in Icodextrin users without diabetes. The adjusted HR of CHF in PD patient with diabetes was 0.62 (95% CI: 0.42, 0.93) for Icodextrin users compared with non-users. Meanwhile, in PD patients without diabetes, the Icodextrin users had adjusted HR of 0.70 (95% CI: 0.50, 0.98) compared with non-users. After adjusting for competing risk of death, Icodextrin users had adjusted (sub-hazard ratio [SHR] of 0.63 (95% CI: 0.42, 0.9) for CHF, compared with non-users in PD patients with diabetes.[14, level II-2]

5.2.8 Effects of Neutral pH, Low-GDP on Peritoneal Membranes

Tawada M, Hamada C, Suzuki Y et al. conducted a case-control study to investigate the long-term effects of neutral pH, low-GDP PD solutions on morphological and functional changes in the peritoneal membrane. The study retrieved 444 peritoneal membrane biopsy samples from a total of 205 patients who had been treated with PD from December 1998 to December 2017. Out of 205 patients, 78 patients used acidic PD solutions (control) and 127 patients used only neutral pH solution (intervention) without

history of treatment with acidic solution. The collected samples were assessed for two main pathological characteristics; thickness of peritoneal membrane and vasculopathy (L/V ratio). The thickness of peritoneal sub-mesothelial compact zone in the conventional group was significantly greater than in the pH-neutral group; 375.0; (95% CI: 274.06, 602.00) vs 244.0; (95% CI 154.68, 390.25); $p < 0.001$. As for long term, D/P Cre in conventional group was also significantly higher than in neutral-pH group; 0.70 ± 0.14 and 0.61 ± 0.12, $p = 0.008$, respectively. The peritoneal thickness was significantly higher in the conventional group compared to the pH-neutral group, $p < 0.05$. As for vasculopathy, the L/V ratio was significantly lower in conventional group compared to neutral pH group; 0.50 ± 0.17 and 0.76 ± 0.06, $p < 0.001$, respectively. The formation of new membrane and fibrin deposition also higher in conventional group than in neutral pH group. The long-term effect also showed similar effect where the conventional group was significantly higher than in neutral pH group, $p<0.01$. The authors also look at any relationship between PD duration and pathological changes. The study showed no correlation between peritoneal thickness and PD duration in both groups. However, the L/V ratio was significantly decreased over time in conventional group ($r = -0.359$, $p = 0.008$) but in neutral pH group, the vasculopathy did not progress over time. Another assessment was relationship between peritoneal function and pathological changes. The authors assessed the correlation between peritoneal permeability (D/P Cre) and pathological changes and the data used were on D/P Cre which assessed within one year before the catheter removal. Meanwhile the D/P Cre correlate negatively with L/V ratio ($r – 0.832$, $p = 0037$) in the conventional group and not related in neutral-pH group. In addition, neither peritoneal thickness nor number of CD31 positive vessels correlated with D/P Cre. The authors concluded that, neutral pH PD solution can reduce the peritoneal morphological and functional deterioration with long-term PD treatment.[15, level II-2]

5.2.9 Effects on MIA syndrome

Stankovic-popovic A et al. conducted a cross-sectional study to evaluate the effects of PD solutions (standard PD solution versus biocompatible PD solution) on some parameters of MIA syndrome (chronic inflammation, malnutrition and atherosclerosis) in patients undergoing CAPD. The study was conducted in Military Medical Academy Belgrade where patients were treated by CAPD according to mode of insurance. Only 42 patients were recruited in the study and were grouped equally according to type of insurance covered; CAPDDP-1 (patients with civil insurance and used bio-incompatible PD solution) and CAPDP-2 (patients covered with military insurance and used biocompatible PD solution). After 3.1 ± 0.4 year for CAPDP-1 and 3.5 ± 0.5 year for CAPDP-2 group, the inflammatory markers in serum and peritoneal effluent were analysed. There was no significant difference between both groups in term of serum ferritin and fibrinogen, serum and effluent level of IL-1, IL-6 and TNF-α in CA-125 effluent level, total serum cholesterol, triglycerides, bicarbonates, albumin and BMI, peritonitis incidence, mean ejection fraction and in frequency of vulvular calcification. The difference was showed in mean value of serum hs-CRP where CAPDP-2 group was significantly lower than CAPDP-1 group. The CAPDP-1 group had significantly worst nutritional status than patients in CAPDP-2 group which was determined by mid-arm circumference, mid-arm muscle circumference and SGA.[16, level II-1]

5.3 ORGANISATIONAL

5.3.1 PD Technique Survival/Technique Failure

a) Neutral pH, Low GDP versus Conventional Glucose PD

Htay H et al. reported that, there was low certainty evidence (15 studies, 1,229 participants) showed that neutral pH, low GDP PD solution may make little or no difference to death-censored technique failure, although overall participant numbers were relatively small for assessing this outcome; RR: 1.10, 95% CI: 0.75, 1.63; I^2 = 0%.[10, level 1]

b) Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution

Kanno A. et al. reported in their SR with MA, an overall effect of icodextrin on technical survival was not significant in five RCTs of 470 patients (RR 0.57; 95% CI 0.29, 1.12; p = 0.10, I^2 = 0%; low certainty evidence).[21, level 1]

Based on Goosen K et al. SR with MA, the PD technique survival was no defined consistently throughout studies, thus they analysed the number of conversions to HD. The authors reported that there was no difference between icodextrin and glucose overall (Peto OR, 0.77 [95% CI 0.39,1.50]; moderate certainty) or for any subgroups (<6 weeks, 1.06 [95% CI0.07, 17.03]; three to six months 0.59 [95% CI 0.23, 1.54]; one to two years, 0.98 [95% CI 0.36, 2.68]; incident patients, 1.29 [95% CI 0.28, 6.03], prevalent patients 0.81 [95% CI 0.35, 1.84]; diabetic patients 1.97 [95% CI 0.50, 7.69] or non-diabetic patients 0.98 [95% CI 0.27, 3.60]. The absolute control-group rate of conversion to HD was 29 per 1,000 patients. The overall certainty of the evidence was assessed to be moderate. The number of patients who received kidney transplant was balanced between groups. [20, level 1]

Meanwhile, Htay H et al. stated that majority of studies (four studies with 350 participants) had short follow-up duration (less than six months) and low event numbers, thus it was uncertain whether the used of Icodextrin led to any differences in technique failure; RR: 0.60, 95% CI: 0.32, 1.12, I^2 =0%.[10, level 1]

Han SH et al. found in the study, the causes of technique failure were peritonitis, non-compliance and ultrafiltration. Out of three causes, the non-compliance in Icodextrin group had significantly lower technique failure than non-Icodextrin group; 0.6% versus 2.0%; p = 0.048.[12, level II-2]

5.3.2 Hospitalisation

a) Neutral pH, Low GDP versus Conventional Glucose PD

The SR and MA by Htay H et al. reported that there was very low certainty evidence (two studies of 230 participants) for this outcome was unsure whether neutral pH, low GDP PD solution reduced the duration of hospitalisation.[10, level 1]

Sikaneta T. et al. also reported that there were no differences between neutral pH, low GDP group and conventional PD solution group for hospitalisations (24 [54%]) and 21 [46%], respectively, p = 0.48).[11, level 1]

5.3.3 Health-Related Quality of Life (HRQoL)

Goossen K et al. assessed the HRQoL which were obtained from two RCTs with 12 months' duration. The HRQoL was assessed based on 36-Item Short Form Health Survey (SF-36) generic questionnaire physical and mental component summaries; disease-specific modules' overall score. The results of mean difference (MD) for Physical Component Summary score was 0.95 [95% CI -2.96, 4.86], for Mental Component Summary score MD 0.33 [95% CI -7.41, 8.06] and the overall score of disease-specific modules MD 0.60 [95% CI -4.93, 6.13] were inconclusive. No subgroups analyses were performed due to the small number of contributing studies.[20, level 1]

5.4 SAFETY

5.4.1 Adverse Events (AEs) & Peritonitis Incidence

a) Neutral pH, Low GDP versus Conventional Glucose PD

There was limited evidence (six studies with 519 participants) reported in SR and MA by Htay H et al. regarding adverse events of neutral pH, low GDP versus conventional glucose PD. The authors found uncertain evidence whether the neutral pH, low GDP PD solution led to any differences in adverse events compared with conventional PD solutions. In low certainty evidence (12 studies, with total of 1,055 participants), Htay H et al. reported, the neutral pH, low GDP PD solution may make little or no difference to the peritonitis incidence compared with conventional PD solution; RR 1.26, (95% CI: 0.92, 1.72; I^2 = 69%). In term of peritonitis rate, 10 studies (18,184 participants) reported no difference between both PD solution; RR 1.18, (95% CI: 0.84, 1.64; I^2 = 67%). However, in sub-analysis, the incidence of peritonitis was lower in the neutral pH, low GDP solution group in studies with low risk for attrition bias (three studies with total of 359 participants; RR 0.65, 95% CI: 0.47, 0.90; I^2 = 0%.[10, level 1]

Sikaneta T. et al. reported that there were no differences between neutral pH, low GDP group and conventional PD solution group (two deaths in each groups). [11, level 1]

b) Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution

Kanno A. et al. showed that overall peritonitis rates did not significantly differ between icodextrin and glucose PD solutions in eight RCTs of 1,034 patients (RR 0.95; 95% CI 0.79, 1.15; p = 0.62, I^2 = 0%; low certainty evidence). The authors also reported that the occurrence of rash elicited by icodextrin and glucose PD solutions did not significantly differ in four RCTs of 855 patients (RR 1.84; 95% CI 0.48, 7.09; p = 0.35, I^2 = 46%; low certainty evidence).[22, level 1]

Goossen K et al. reported in moderate to high certainty of evidence, the safety outcomes for icodextrin were similar to glucose including the number of serious AEs (RR 0.91 [95% CI 0.76, 1.10], total AEs (RR 1.04 95% [0.94, 1.16], AEs leading to withdrawal (RR 0.87, [95% CI 0.65, 1.17], hospitalizations (RR 0.81 [95% CI 0.64, 1.04] and peritonitis (RR 1.08 [95% CI 0.88, 1.32].[21, level 1]

In low certainty evidence (six studies, 667 participants), Htay H et al. reported that Icodextrin may make little or no difference to peritonitis incidence; RR 0.95, (95% CI: 0.77, 1.18; I^2 = 0%).[10, level 1]

In low certainty evidence (three studies, 755 participants), Htay H et al. reported that Icodextrin may make little or no difference to the risk of rash compared with glucose exchanges; RR 2.51, (95% CI 0.59,10.72; I^2 = 38%). In very certainty evidence (five studies, 816 participants), it was uncertain whether Icodextrin use led to any differences in adverse events.[10, level 1]

5.5 COST/COST-EFFECTIVENESS

There was no retrievable evidence specifically on economic evaluation of biocompatible PD solution. However, there was one budget impact analysis of HD and PD, two cost analysis on ESRD expenditure in Malaysia and one cost utility study comparing HD and CAPD in Malaysia. According to MOH nephrologist, the price of the biocompatible PD solution was estimated around RM 25.30 per bag of neutral pH, low GDP, and RM60.00 per bag for Icodextrin 7.5%. Meanwhile for conventional PD solution, the price is cheaper which is RM15.50 per bag.

Bavanandan S. et al. conducted budget impact analysis to investigate the five years' health care budget impact of variable distribution of adult patients treated with peritoneal dialysis (PD) and in-centre haemodialysis (ICHD) on government funding in Malaysia. Epidemiological data including dialysis prevalence, incidence, mortality, and transplant rates from the Malaysian renal registry reports were used to estimate the dialysis patient population for the next 5 years. The baseline scenario assumed a stable distribution of PD (8%) and ICHD (92%) over 5 years. Alternative scenarios included the prevalence of PD increasing by 2.5%, 5.0%, and 7.5% or decreasing 1% yearly over 5 years. Under the current best available cost information, an increase in the prevalent PD population from 8% in 2014 to 18%, 28%, or 38% in 2018 is predicted to result in five years cumulative saving of RM 7.98 million, RM15.96 million, and RM23.93 million, respectively, for the Malaysian government. If the prevalent PD population decrease from 8% in 2014 to 4.0% in 2018, the total expenditure for dialysis treatments would increase by RM3.19 million over the next 5 years. In conclusion under the current cost information associated with PD and HD paid by the Malaysian government, increasing the proportion of patients on PD could potentially reduce dialysis-associated costs in Malaysia.[17]

Bujang MA et al. conducted an analysis to describe the trend of incidence and prevalence of ESRD patients in Malaysia from 1993 to 2013. The study also aims to determine the best univariate forecasting model to predict the incidence and prevalence of persons with ESRD until the year 2040. The authors also reported that based on a local study in 2001, the cost of dialysis treatment was estimated to be RM 30,000 (USD 7,500) per patient, per year. The cost per patient was estimated to be within RM 29,092 to RM 33,642. Based on their current model analysis, the estimated incidence of new dialysis patients in Malaysia in 2020 is 10,208 cases and 19,418 in 2040. Meanwhile, the estimated prevalence is 51,269 and 106,249 cases in 2020 and 2040, respectively. With such projected prevalence, the authors estimated costs for the treatment were USD 384,517,500 and USD 796,867,500 in the years 2020 and 2040.[18]

Current cost analysis by Ismail H (2019) was to determine the total expenditure of ESRD by the public sector in Malaysia and examined how it has affected the total public sector expenditure on health. The overall finding of the analysis showed that the total public sector expenditure on ESRD over period of seven years (2010-2016) was RM5.76 billion (USD4.03 billion) of which the MOH was the main contributor (55%). Out of that amount, 94% was spent on dialysis and the other 6% was spent on renal transplant. The spending was on reimbursement on dialysis centres either in public or private centres. The distribution of type of ESRD expenditure by year was provided in figure below.[3]

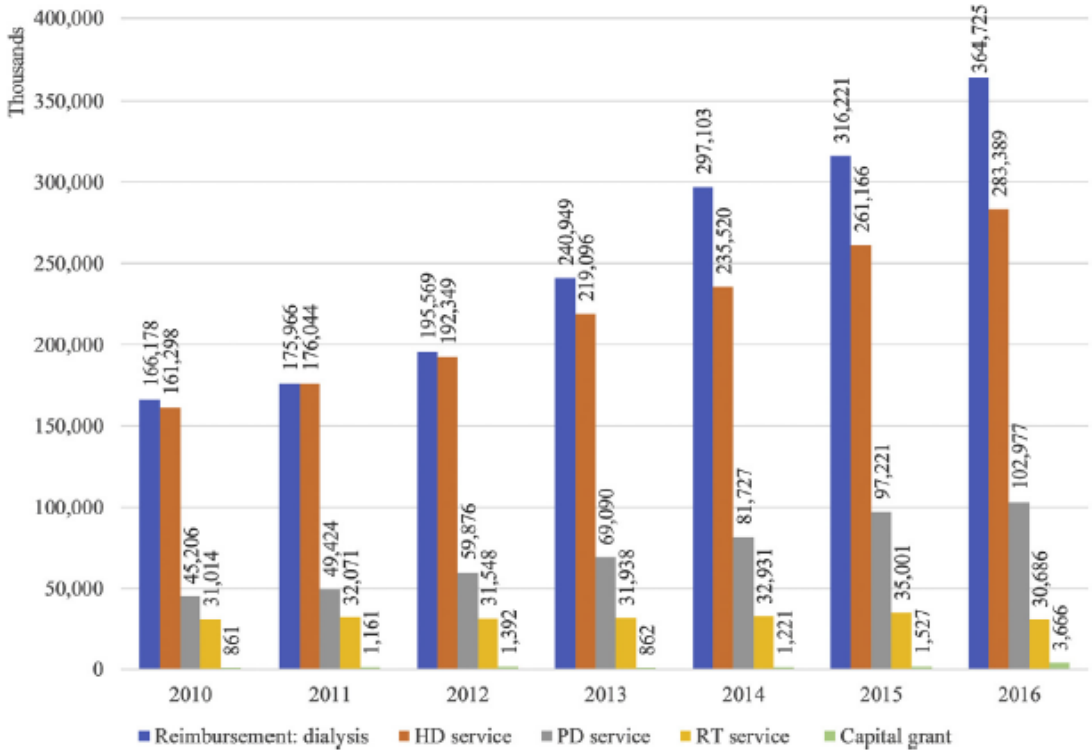

Figure 5: Distribution of ESRD expenditure by public sector in Malaysia (2010-2016) by category of expenditure (US dollars purchasing power parity).[3]

Surendra NK et al. conducted an economic evaluation to compare the cost utility of HD and CAPD in Malaysia and to assess the cost utility of different dialysis provision strategies at varying levels of CAPD usage versus current practice using a Markov Model simulation cohort. The model was conducted based on Ministry of Health perspective with temporal horizons of five years. The base case scenario was 60% HD and 40% CAPD. The model had considered three scenarios. Scenario 1 was a model with an increased initial distribution of CAPD by 5% (55% HD and 45% CAPD), Scenario 2 was a model with an increased initial distribution of CAPD by 10% (50% HD and 50% CAPD) and Scenario 3 was a model with a decreased initial distribution of CAPD by 10% (70% HD and 30% CAPD). In 2017, Malaysia GDP per capita was US$9,660 (~ RM40,000), so to be cost-effective the cost per life years (LY) or quality adjusted life years (QALY) of this model should be lower than RM120,000 per patient. The cost per LY for patients on HD was RM39,791, slightly higher than the cost per LY for patient on CAPD (RM37,576). The cost per QALY for patient in HD was RM46,595 and RM41,527 for patient in CAPD. The Markov model cohort simulation showed commencement of

CAPD in 50% of ESRD patients as initial dialysis modality was very cost-effective versus current practice of 40% within MOH. The results for each scenario were in Table 9. Reduction in CAPD use was associated with higher cost and small devaluation in QALYs.[19]

Table 6: Costs, Outcome and Cost-Effectiveness[20]

Costs and outcomes	Base case	Scenario 1	Scenario 2	Scenario 3
HD:CAPD ratio	**60:40**	**55:45**	**50:50**	**70:30**
Undiscounted				
Projected cost, RM	313,412	308,032	307,014	311,086
Total LYs	8.005	7.910	7.902	7.933
Total QALYs	7.113	7.037	7.041	7.025
Discounted (3%)				
Projected cost, RM	94,425	93,517	93,236	94,361
LYs	2.417	2.407	2.407	2.410
QALYs	2.150	2.145	2.148	2.136
Cost effectiveness				
Cost per LY (discounted)	39,074	38,844	38,740	39,156
Cost per QALY (discounted)	43,919	43,591	43,399	44,172
Cost per LY (undiscounted)	39,151	38,943	38,852	39,214
Cost per QALY (undiscounted)	44,059	43,774	43,606	44,281
ICER				
Per LY (discounted)	120,160	355,207*	-	355,207*
Per QALY (discounted)	734,979	-92,909*	-	-92,909*
Per LY (undiscounted)	62,090	132,108*	-	132,108*
Per QALY (undiscounted)	87,864	-264,922*	-	-264,922*

ICER-incremental cost effectiveness ratio, QALY-quality-adjusted life year, LY-life Year

*"dominated" (worse outcomes, higher costs)

5.5 LIMITATIONS

This technology review has several limitations. Although there was no restriction in language during the search, but only English full text articles were included in this report. Some of the included study had small samples size which may not give conclusive results.

Table 7: Summary of Biocompatible PD Solution Outcomes

No	Outcome	Neutral pH, Low GDP versus Conventional Glucose PD	Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution/ no Icodextrin
1.	Residual Renal Function/ Urine Volume Fluid Overload	Neutral pH and low GDP PD solution improved the preservation of RRF compared to standard PD solution while the conventional PD solution group showed decline RRF (high certainty evidence) → (SMD 0.19 [95% CI 0.05, 0.33; I^2 = 0%] High urine volume with neutral pH, low GDP as compared to conventional PD solution– improved overtime (high certainty evidence) → (MD 114.37ml/d [95% CI: 47.09, 181.65; I^2=3%]) after 12 months Urine volume declined by 30ml/month in biocompatible PD solution group and 39ml/month in conventional PD solution group and oliguria also reported less frequent in biocompatible PD solution	No difference of RRF using Icodextrin (Moderate certainty) → (MD 0.56mL/min [95% CI -0.37 to 1.49]; p = 0.24, I^2 = 0) Decreased fluid overload→ Icodextrin significantly decreased the frequency of reported episodic uncontrolled peritoneal fluid overload (RR 0.31 [95% CI 0.12, 0.82] p = 0.02, I^2 = 0%) at moderated certainty evidence Not associated with urine volume (MD 106.08mL/day [95% CI -173.29, 385.45] p = 0.13; I^2 = 39%) → low certainty evidence Urine volume showed little increase but not significant with Icodextrin (low certainty evidence) → (MD -88.88mL/d [95% CI: -356.88,179.12] p= 0.5; I^2 = 0%) • 1 RCT reported that 6 months used of Icodextrin had better maintenance of urine volume when compared to 2.27% dextrose PD solution • 1 RCT showed significant higher daily urine volumes than glucose dialysate at 12 months
2.	Peritoneal Ultrafiltration (UF) capacity	After 4 hours, neutral pH, low GDP group showed a lower UF capacity than conventional PD solution (low certainty evidence) → (SMD -0.42 [95% CI: -0.74, -0.10]; I^2 = 51%) and minimal changes in peritoneal membrane and MIA syndrome (chronic inflammation, malnutrition and atherosclerosis). At 24 months of follow-up, low glucose group showed a non-significant decrease but significant decrease in high glucose group.	Icodextrin did not lead to a significant increase in UF (MD 186.76mL/day [95% CI -47.08, 420.59] p = 0.12, I^2 = 64%] at low certainty evidence • More effective for up to 6 months (MD 208.92 [95% CI 99.69-318.14mL/24h]) with high certainty of evidence, but no difference in the long-term • Uniformly improved peritoneal UF (MD 448.54 mL/24h [95% CI: 289.28, 607.80] I^2 = 0%)
3.	Peritoneal Solute Transport Rate	After 4 hours' dialysate plasma creatinine ratio was higher in neutral pH, low GDP patients compared to conventional glucose PD (low certainty evidence) → (MD 0.01 [95% CI 0.00, 0.003); I^2 = 1%] Subgroup analysis showed no	Not affect the D/P Cr (MD 0.001 [95% CI -0.07, 0.07] p = 0.97, I^2 = 65%); very low certainty evidence as there was insufficient evidence)

No	Outcome	Neutral pH, Low GDP versus Conventional Glucose PD	Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution/ no Icodextrin
		difference after 4 hours of dialysate There was an increase in mean solute transport in low glucose group (not significant) and significant increase in high glucose group	
4.	Peritoneal Small Solute Clearance	No difference in peritoneal creatinine clearance and peritoneal urea clearance • Peritoneal creatinine clearance (MD -0.44 L/week/1.73m_2, [95%, CI: -2.03, 1.15]; I^2 = 0%) or • Peritoneal urea clearance (MD -0.01, [95%, CI: -0.12, 0.09]; I^2 = 26%)	No difference to peritoneal creatinine clearance (low certainty evidence) → (SMD 0.36 [95% CI: 0.24, 0.96] I^2 = 66%)
5.	Peritonitis	No difference in peritonitis incidence (RR 1.26 [95% CI 0.92, 1.72; I^2 = 69]) and peritonitis rate (RR 1.18 [95% CI 0.84, 1.64] I^2 = 67%) When classified according to attrition bias – lower incidence compared to conventional solution	Incidence: No difference (RR 1.08 [95% CI 0.88, 1.32]) Rate: Not significantly differ (RR 0.95 [95% CI 0.79, 1.15] p = 0.62; I^2 = 0%) □ low certainty evidence
6.	Inflow Pain	Uncertain	NA
7.	Patient Survival	No difference to death (low certainty evidence) → (RR 0.73 [95% CI: 0.47, 1.14]; I^2 =0%)	Not significantly differ (RR 0.75 [95% CI 0.33, 1.71] p = 0.49, I^2 = 0%) Uncertain (RR 0.82 [95% CI: 0.32, 2.13] I^2 = 0%) Probably decreased mortality risk (Peto OR, 0.49 [95% CI 0.24, 1.00]) and for causes of death with moderate heterogeneity • Lower risk of death (HR 0.69 [95% CI 0.53, 0.90] p = 0.006)
8.	Cardiovascular: CHF	NA	Incidence rate of CHF was 26% lower in Icodextrin users than in non-users (13.7% [95% CI: 12.4, 15.1] vs 18.6 [95% CI: 16.6, 20.9] per 1000 person-years; respectively) The highest CHF rate was 28.5 (95% CI: 22.8, 35.4) per 1000 person-years in Icodextrin non-users with diabetes but in Icodextrin users with diabetes, the rate was reduced to 17.8 (95% CI: 15.3, 20.7) per 1000 person-years or to 11.0% (95% CI: 9.56,12.7) per 1000 person-years in Icodextrin users without diabetes Adjusted HR of CHF in PD patient

No	Outcome	Neutral pH, Low GDP versus Conventional Glucose PD	Glucose Polymer (Icodextrin) versus Conventional Glucose PD Solution/ no Icodextrin
			with diabetes was 0.62 (95% CI: 0.42, 0.93) for Icodextrin users compared with non-users
10.	Cardiovascular – structure & function	NA	No difference (require more study)
11.	Peritoneal Membrane	Membrane thickness: conventional PD solution = thicker overtime compared to neutral pH solution Vasculopathy (L/V ratio) = lower in conventional group overtime compared to neutral H solution	NA
12.	MIA syndrome (chronic inflammation, malnutrition and atherosclerosis)	Significantly good compared to conventional PD solution	NA
13.	Technique Survival	No difference to death-censored technique failure (RR 1.10 [95% CI: 0.75, 1.63]; I^2 = 0%) → in low certainty evidence	Overall effect was not significant (RR 0.57 [95% CI 0.29, 1.12] p = 0.10, I^2 = 0%) □ low certainty evidence No difference (Peto OR, 0.77 [95% CI 0.39,1.50] □ moderate certainty) Uncertain (RR: 0.60 [95% CI: 0.32, 1.12] I^2 =0%)
14.	Hospitalisation	No differences (24 [54%]) vs 21 [46%] in control, p=0.48)	

***NA = not available * '•' = findings that differ from the main result**

6. CONCLUSION

Efficacy / Effectiveness

Based on the above review, the evidence showed that neutral pH, low GDP PD solution was better compared to conventional PD solution in improving the residual renal function (RRF) or urine volume. However, for Icodextrin, the RRF showed no significant difference compared to conventional PD solution in SR and MA but a little increase and better improvement in another studies after six months. Another main outcome was on cardiovascular events, the Icodextrin solution showed an improvement in coronary heart failure (CHF). The cumulative incident CHF was lower in Icodextrin users than non-users. Besides, the CHF incidence rate also greater in diabetic patient without using Icodextrin subgroups than in diabetic patient who were using Icodextrin PD solution. The hazard ratio of CHF in diabetes patient on Icodextrin also lower compared to diabetes patient without Icodextrin PD solution. On the other hand, Icodextrin showed no significant difference in any changes in cardiovascular structure and function, however, this finding requires further study.

On the other hand, for other outcomes the evidence varied and most of the findings was at low certainty evidence. The biocompatible or neutral pH, low GDP PD solution showed lower peritoneal ultrafiltration compared to conventional PD solution after four hours of PD, minimal changes in peritoneal membrane and MIA syndrome (chronic inflammation, malnutrition and atherosclerosis). However, for Icodextrin, the included study showed there was an increase trend but not significant in ultrafiltration capacity. There was also no significant difference in peritoneal small solute clearance, peritonitis

rate and patient survival between biocompatible or neutral pH, low GDP PD solution and Icodextrin. Meanwhile, findings for inflow pain and hospitalisation was uncertain in all biocompatible PD solutions.

Organisational Issue

The above review showed that there was no difference to death-censored technique failure between neutral pH, low GDP PD solution and conventional PD solution. Meanwhile for Icodextrin, the technique failure was uncertain except one study showed that non-compliance in Icodextrin group was significantly lower that non-Icodextrin group.

Safety

Safety issue for both neutral pH, low GDP and Icodextrin PD solution was uncertain.

Cost

No economic evaluation comparing biocompatible PD solution and conventional PD solution retrieved. The economic evaluation papers retrieved showed that peritoneal dialysis was cost saving over haemodialysis.

8. REFERENCES

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9. APPENDIX

9.1. Appendix 1: LITERATURE SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and OvidMEDLINE® 1946 to present

1 Peritoneal Dialysis/ (17568)
2 Dialysis Solutions/ (4614)
3 (peritoneal adj1 dialys#s).tw. (24384)
4 (dialys#s adj1 solution$).tw. (1399)
5 dialy#ates.tw. (1415)
6 peritoneal dialysis solution.mp. (314)
7 PD solution.mp. (245)
8 pd solution$.tw. (444)
9 peritoneal dialys#s solution$.tw. (635)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (32340)
11 Biocompatible Materials/ (58163)
12 biocompatible solution.mp. (28)
13 Biocompatible peritoneal dialysis solution.tw. (8)
14 Biocompatible solution$.tw. (100)
15 biocompatible adj1 material$).tw. (1257)
16 (bioartificial adj1 material$).tw. (5)
17 biomaterial$.tw. (30368)
18 (h?emocompatible adj1 material$).tw. (15)
19 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (77767)
20 Icodextrin/ (511)
21 extraneal.tw. (50)
22 Icodextrin.tw. (667)
23 icodial.tw. (0)
24 glucan$.tw. (18013)
25 20 or 21 or 22 or 23 or 24 (18759)
26 Glucose/ or low glucose degradation.mp. (152965)
27 low glucose degradation.tw. (74)
28 glucose.tw. (445935)
29 (anhydrous adj1 dextrose).tw. (5)
30 d glucose.tw. (20170)
31 d-glucose.tw. (20170)
32 dextrose.tw. (11789)
33 (glucose adj1 dL-isomer).tw. (0)
34 (glucose adj1 l-isomer).tw. (0)
35 (glucose adj1 alpha-d-isomer).tw. (0)
36 (glucose adj1 beta-d-isomer).tw. (0)
37 (glucose adj1 monohydrate).tw. (48)
38 l glucose.tw. (3633)
39 l-glucose.tw. (3633)
40 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 (496008)
41 10 and 19 (342)
42 10 and 25 (654)
43 10 and 40 (3288)
44 19 or 25 or 40 (587913)
45 10 and 44 (3577)
46 limit 45 to humans (2829)
47 limit 41 to humans (289)
48 limit 42 to humans (577)
49 limit 43 to humans (2589)
50 limit 46 to yr="2011 -Current" (670)
51 limit 47 to yr="2011 -Current" (85)
52 limit 48 to yr="2011 -Current" (189)
53 limit 49 to yr="2011 -Current" (588)

OTHER DATABASES	
EBM Reviews - Cochrane database of systematic reviews	(Same as above)
EBM Reviews - Health Technology Assessment	
PubMed	
NHS economic evaluation database	Biocompatible PD solution, Icodextrin, low GDP glucose
INAHTA	
FDA	
Others (Google Scholar, Google)	

9.2. Appendix 2

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomised controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

9.4. Appendix 3 EVIDENCE TABLE

EFFECTIVENESS
Evidence Table: Efficacy/Effectiveness
Question: Is it BIOCOMPATIBLE PD SOLUTION effective for peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
1. Kanno A, Tsujimoto Y, Fujii T, Fujikura E, Watanabe K, Yuasa H, Ryuzaki M, Ito Y & Nakamoto H. Comparison of Clinical Effects Between Icodextrin and Glucose Solutions on Outcomes of Peritoneal Dialysis: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Renal Replacement Therapy. 2020; 6:7	SR with MA Objective: To determine the risks and benefits of icodextrin compared with a glucose-based solution with respect to clinically important and patient-centered outcomes. Methods:		•	•			-	

Evidence Table: Efficacy/Effectiveness
Question: Is it BIOCOMPATIBLE PD SOLUTION effective for peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
2. Goossen K, Becker M, Marshall MR, Buhn S, Breuing J, Firanek CA, Hess S, Nariai H, Sloand JA, Yao Q, Chang TI, Chen J, Paniagua R, Takatori Y, Wada J, & Pieper D. Icodextrin versus Glucose Solutions for the Once-Daily Long Dwell in Peritoneal Dialysis: An Enriched Systematic Review and Met-analysis of Randomized Controlled Trials. Am J Kidney Dis. 2020 Jun;75(6):830-846.	SR with MA Objective: To compare once-daily long-dwell icodextrin versus glucose among patients with kidney failure undergoing PD Methods:		•	•			-	

Evidence Table: Efficacy/Effectiveness
Question: Is it BIOCOMPATIBLE PD SOLUTION effective for peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
3. Htay H, Johnson DW, Wiggins KJ, Badve SV, Craig JC, Strippoli GFm and Cho Y. Biocompatible Dialysis Fluids for Peritoneal Dialysis. Cochrane Database of Systematic Reviews. 2018; Issue 10. Doi: 10.1002/14651858	SR with MA Objective: To look at the benefits and harms of biocompatible PD solutions in comparison to standard PD solutions in patients receiving PD Methods: Data collection and analysis • 2 authors involved • Summary effects using random-effects model • Results were expressed as risk ratios and 95% CI for categorical variables and MD or SMD and 95% CI for continuous variables Types of Outcome Measures Primary Outcome • Decline in RRF (changes in residual creatinine clearance (CrCl), urea clearance, Kt/V, glomerular filtration ate (GFR) and urine output) • Peritoneal UF (during peritoneal equilibrium test and daily UF) • Peritonitis rate (episodes/y, episode/total patient-		Selection Criteria: • All RCTs and quasi-RCTs in adults and children comparing the effects of biocompatible PD solutions in PD were included 42 eligible studies included (3262 participants • 6 new studies (543 participants • 29 studies (1971 participants) compared neutral pH, low GDP, PD solutions with conventional PD • 13 studies (1291 participants) compared Icodextrin with conventional PD	Biocompatible PD solutions • eutral PH, lactate buffered, low-GDP • eutral pH, bicarbonate (± lactate)-buffered, low GDP • lucose polymer (Icodextrin)	Conventional glucose PD solutions		**RESULTS** Study Quality • Risk of bias: high for sequence generation in 3 studies • Allocation concealment in 3 studies • Attrition bias in 21 studies • Selective outcome reporting bias in 16 studies ***1) Neutral pH, Low GDP vs Conventional glucose PD solution*** a. Residual Renal Function (RRF) - High certainty evidence: - Improved the preservation of RRF (15 studies, 835 participants: SMD 0.19, 95% CI 0.05 to 0.33; I^2 = 0%) - This approximated to a MD in GFR of 0.54ml/min/1.73m^2 (95% CI 0.14 to 0.93) - This effect was presented for all follow-up duration categories analysed: • Up to 12months (11 studies, 722 participants): SMD 0.18, 95% CI 0.05 to 0.32; I^2 = 3%), translated into MD in GFR of 0.59 mL/min/1.73 m^2 (95% CI 0.16 to 1.05), • 12 to 24 months 10 studies, 641 participants): SMD 0.25, 95% CI 0.10 to 0.41; I^2 = 0%), translated into MD in GFR of 0.71 mL/min/1.73 m^2 (95% CI 0.28 to 1.16) and • More than 24 months (6 studies, 343 participants): SMD 0.30, 95% CI 0.08 to 0.51; I^2 = 0%), translated into MD in GFR of 0.85 mL/min/1.73 m^2 (95% CI 0.23 to 1.44), respectively.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
	months on PD) and incidence (number of events/follow-up period) • Technique survival (number of participants remaining on PD at study completion) • Patient survival (number of participants alive at study completion) • Toxicity/adverse events (rahs, uncontrolled fluid overload etc) Secondary Outcome • Inflow pain • Changes in peritoneal membrane transport (4-hr dialysate: plasma creatinine) • Dialysis adequacy (CrCc, Kt/V) • Hospitalisation (number of hospitalization days during study follow-up period)						- Subgroup analysis was performed on PD fluid types. This analysis was limited by the fact that the majority of studies used only one solution type (Balance®) such that no useful conclusions could be drawn b. Urine Volume - High certainty evidence: daily residual diuresis was higher in neutral pH, low GDP solution - (11 studies, 791 participants): MD 114.37 mL/d, 95% CI 47.09 to 181.65; I^2 = 3%) - No difference in urine volume up to 12 months' follow-up (10 studies, 819 participants): MD 69.72 mL/d, 95% CI -55.95 to 195.40; I^2 = 60%) - The benefit was observed with greater than 1 year follow-up durations: • 12 months to 24 months: (8 studies, 579 participants): MD 110.57 mL/d, 95% CI 40.81 to 180.34; I^2 = 0%) and • More than 24 months: (3 studies, 279 participants): MD 169.22 mL/d, 95% CI 23.98 to 314.46; I^2 = 0%) - Subgroup analysis was performed on PD fluid types (limited by the fact that the majority of trials used only one solution type (Balance®) → no useful conclusions could be drawn - Proportion of patients who developed anuria was not different between the 2 groups (2 studies 246 participants): RR 0.56, 95% CI 0.18 to 1.75; I^2 = 60%) c. Peritoneal Ultrafiltration - The 4 hrs peritoneal UF measured during a peritoneal equilibration test may be lower in the neutral pH, low GDP solution (9 studies, 414	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
							participants): SMD -0.42, 95% CI -0.74 to -0.10; I^2 = 51%; the estimated MD -69.72 mL/4 hours, 95% CI -122.84 to -16.60; low certainty evidence) - Moderate heterogeneity, which could not be explained by differences in study design, study population, or risk of bias. - Outcomes from daily peritoneal UF analysis could not be reported due to high heterogeneity (I^2 = 82%). d. Peritoneal Solute Transport Rate - The 4 hrs dialysate: plasma creatinine ratio (D/P_{Creat}) measured during a peritoneal equilibration test may be higher in the neutral pH, low GDP solution group (10 studies, 746 participants): MD 0.01, 95% CI 0.00 to 0.03; I^2 = 1%; low certainty evidence) - However, subgroup analysis with patient characteristics fluid types and study design showed no significant difference in 4 hrs D/PCreat values between the neutral pH, low GDP solution and control groups. e. Peritoneal Small Solute Clearance - Neutral pH low GDP PD solution may make little or no difference to peritoneal creatinine clearance (7 studies, 510 participants):MD-0.44 L/week/1.73m^2, 95%CI -2.03 to 1.15; I^2 = 0%) or - peritoneal urea clearance (6 studies, 422 participants): MD -0.01, 95% CI -0.12 to 0.09; I^2 = 26%; - Low certainty evidence between treatments using and conventional PD solution. f. Peritonitis	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
							- Neutral pH, low GDP and conventional PD solution groups may make little or no difference to the incidence of peritonitis (12 studies, 1055 participants): RR 1.26, 95% CI 0.92 to 1.72; I^2 = 69%; low certainty evidence - No difference to peritonitis rate (10 studies, 18,184 patient-months): RR 1.18, 95% CI 0.84 to 1.64; I^2 = 67%; low certainty evidence) - Moderate level of heterogeneity for both analyses and when studies were classified according to the risk of attrition bias, the incidence of peritonitis was lower in the neutral pH, low GDP solution group in studies with a low risk for attrition bias (3 studies, 359 participants): RR 0.65, 95% CI 0.47 to 0.90; I^2 = 0%). g. Inflow Pain - In very low certainty evidence, it is uncertain whether neutral pH, low GDP solution use led to any differences in, may decrease the incidence of inflow pain (1 study, 58 participants): RR 0.51, 95%CI 0.24 to 1.08). - Two additional cross-over RCTs reported significantly lower risk of inflow pain with its use (Fusshoeller 2004; Mactier 1998) - In the study by Mactier 1998, bicarbonate/lactate-buffered PD solution may have had a more favourable effect on inflow pain than purely bicarbonate-buffered PD solution h. Hospitalisation - In very low certainty evidence, it is unsure whether neutral pH, low GDP PD solutions reduce the duration of	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
							hospitalisation (2 studies, 230 participants): MD 3.02 days, 9 CI -7.08 to 13.12; I^2 = 45%). i. Technique Failure - In low certainty evidence neutral pH, low GDP PD solutions may make little or no difference to death-censored technique failure, although overall participant numbers were relatively small for assessing this outcome (15 studies, 1275 participants): RR 1.10, 95% CI 0.75 to 1.63; I2 = 0%). j. Patient Survival - In low certainty evidence neutral pH, low GDP PD solutions may make little or no difference to death (all causes), although overall participant numbers were relatively small for assessing this outcome (15 studies, 1229 participants): RR 0.73, 95% CI 0.47 to 1.14; I^2=0%). k. Adverse Events - In very low certainty evidence, it is uncertain whether neutral pH, low GDP PD solutions use led to any differences in adverse events compared with conventional PD solutions (6 studies, 519 participants) (balANZ 2010; Coles 1997; EURO-BALANCE 2004; Feriani 1998; Schmitt 2002; Tranaeus 2000) ***2) Glucose Polymer (Icodextrin) vs Conventional glucose PD solution*** a. Peritoneal ultrafiltration - In moderate certainty evidence, Icodextrin uniformly augmented peritoneal UF compared with glucose exchanges (4 studies, 102	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
							participants): MD 448.54 mL/d, 95% CI 289.28 to 607.80; I^2 = 0%) - 1 of these 4 studies allowed the use of hypertonic glucose PD solution (3.86%) in the control group (Finkelstein 2005) • 92 APD patients with higher peritoneal solute transport rate (defined as D/PCreat > 0.7) and UF failure (defined as four-hour net UF < 100mL using 2.5% dextrose), Icodextrin resulted in a higher net UF volumes (+373.8 ± 58.9 mL/d) compared with 4.25% dextrose (-239.7mL ± 151.0mL/d) in the controls. - Lin 2009a reported the use of Icodextrin was compared to 2.5% dextrose PD solution according to the peritoneal equilibration test category, • Increases in UF capacities in all patients except low transporters. • Patients with higher peritoneal transport characteristics derived greater UF benefit. b. Episodes of uncontrolled fluid overload - In moderate certainty evidence, Icodextrin probably reduced reported episodes of uncontrolled fluid overload (2 studies, 100 participants): RR 0.30, 95% CI 0.15 to 0.59; I^2 = 0%). c. Residual renal function - In low certainty evidence, Icodextrin may make little or no difference to RRF (4 studies, 114 participants): SMD 0.12, 95%CI -0.26 to 0.49, P = 0.5; I^2 = 0%) - This approximated to a mean difference in renal CrCl of 0.30 mL/min (95% CI - 0.65 to 1.23).	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
							d. Urine volume - In low certainty evidence, Icodextrin-induced increase in peritoneal UF volumes may make little or no difference to daily urine volumes (3 studies, 69 participants):MD-88.88mL/d, 95% CI -356.88 to 179.12, P = 0.5; I^2 = 0%). - Davies 2003 reported better maintenance of urine volume with the use of Icodextrin at six months when compared to 2.27% dextrose PD solution use e. Peritoneal small solute clearance - In low certainty evidence, Icodextrin may make little or no difference to peritoneal CrCl (3 studies, 237 participants): SMD 0.36, 95% CI -0.24 to 0.96; I^2 = 66%; estimated MD 0.36 mL/min 95% CI 0.24 to 0.95) - Two studies were open-label in design with unclear description of the number of participants in each peritoneal equilibration test category (Plum 2002; Posthuma 1997). - Lin 2009a also reported greater peritoneal CrCl measurements in all participants except low transporters. f. Peritonitis - In low certainty evidence, Icodextrin may make little or no difference to peritonitis incidence (6 studies, 667 participants): RR 0.95, 95% CI 0.77 to 1.18; I^2 = 0%) g. Technique Failure - The majority of studies had short follow-up duration (less than six months) and low event numbers - Uncertain whether Icodextrin use led to any differences in technique failure (4 studies, 350 participants): RR	

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							0.60, 95% CI 0.32 to 1.12, I^2 =0%; very low certainty evidence) h. Patient Survival - In the context of low event numbers and short follow-up durations, it is uncertainty whether Icodextrin improves patient survival (6 studies, 816 participants): RR 0.82, 95%CI 0.32 to 2.13; I^2 = 0%; very low certainty evidence i. Adverse Event - In low certainty evidence, Icodextrin may make little or no difference to the risk of rash compared with glucose exchanges (3 studies, 755 participants): RR 2.51, 95%CI 0.59 to 10.72; I^2 = 38%) - In very certainty evidence, it is uncertain whether Icodextrin use led to any differences in adverse events (5 studies, 816 participants) (Lin 2009a; MIDAS 1994; Paniagua 2008; STARCH 2015; Wolfson 2002)	

Evidence Table: Efficacy/Effectiveness
Question: Is it BIOCOMPATIBLE PD SOLUTION effective for peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
4. Wang IK, Lin CL, Yen TH, Lin SY, Yao-Lung L & Sung FC. Icodextrin Reduces the risk of Congestive Heart Failure in Peritoneal Dialysis Patients. Pharmacoepidemiol Drug Saf. 2018; 1-6	Retrospective Cohort? Obj: To investigate whether Icodextrin treatment could reduce the risk of congestive heart failure (CHF) in PD patients This study compared risks of new-onset CHF between PD patients with and without Icodextrin treatment Methods - The data is from insurance claims data of Taiwan National Health Insurance program Statistical Analysis -		5462 PD patients (2931 Icodextrin users and 2531 non-users) Criteria - Newly diagnosed ESRD patients aged 18 years of age and above with PD treatment > 90 days (1 Jan 2005 to 31 Dec 2010) - The date of PD initiation was defined as the index date - Patients who received Icodextrin treatment for > 30 days were defined as the users of the treatment - Related comorbidities were identified for both groups before the end of follow-up were stroke, diabetes, coronary artery disease, hypertension and hyperlipidaemia	With Icodextrin	Without Icodextrin	Study subjects were followed up from index date until the date when CHF were diagnosed or until renal transplantation, death, withdrawal from the insurance or the end of the follow-up (31 Dec 2011)	RESULTS - A total of 735 (25.1%) patients with Icodextrin treatment and 519 (20.5%) patients without Icodextrin treatment switched to HD during the follow-up periods -Icodextrin users were younger than non-users (p = 0.003) with more men and more prevalent with comorbidities and were more likely to use automated PD and to take aspirin, statin, furosemide or bumetanide and clopidogrel CHF incidence -Proportional cumulative incident CHF was lower in Icodextrin users than in non-users (log-rank test P = 0.02) after mean follow-up periods of 3.06 ± 1.65 years and 2.64 ± 1.70 years respectively -After controlling all covariates: the incidence rate of CHF was 26% lower in Icodextrin users than in non-users (13.7%; 95% CI = 12.4-15.1 vs 18.6; 95% CI = 16.6-20.9 per 1000 person-years), the users had an adjusted HR of 0.67 (95% CI = 0.52-0.87), compared with non-users -Demonstration of the CHF risk by diabetes status for the 2 groups: • Incidence rates of CHF were greater in diabetic subgroups than in non-diabetic subgroups • The highest CHF rate was 28.5 (95% CI = 22.8, 35.4) per 1000 person-years in Icodextrin non-users with diabetes → but in Icodextrin users with diabetes, the rate was reduced to 17.8 (95% CI = 15.3-20.7) per 1000 person-years or to 11.0% (95% CI 9.56,12.7) per 1000 person-years	

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							in Icodextrin users without diabetes • In PD patients with diabetes, the adjusted HR of CHF was 0.62 (95% CI = 0.42,0.93) for Icodextrin users compared with non-users • In PD patients without diabetes, the Icodextrin users had adjusted HR of 0.70 (95% CI 0.50, 0.98) compared with non-users • After adjusting for the competing risk of death, Icodextrin users had adjust (sub-hazard ratio [SHR] of 0.63 (95% CI 0.42, 0.9) for CHF, compared with non-users in PD patients with diabetes • Corresponding adjusted SHR was 0.90 in PD patients without diabetes but not significant Conclusion ✓Use of Icodextrin PD solution could benefit PD patients by reducing the risk of new-onset CHF ✓Particularly effective for PD patients with diabetes ✓But require further study	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
5. Tawada M, Hamada C, Suzuki Y, Sakata F, Sun T, Kinashi H, Kasuno T et al. Effects of Long-Term Treatment with Low-GDP, pH-Neutral Solutions on Peritoneal Membranes in Peritoneal Dialysis Patients. Clin Exp Nephrol. 2019 May;23(5):689-699	Obj: to investigate the long-term effects of pH-neutral PD solutions on morphological and functional changes in the peritoneal membrane Method Samples: - 444 peritoneal membrane biopsy samples taken from patients treated with PD (205 include, 239 excluded) Setting - Nagoya University Hospital, hospitals affiliated with Nagoya University and Juntendo University Hospital Sampling time - December 1998 to December 2017 Biopsy Sampling - Peritoneal tissue samples were collected from anterior abdominal wall at the time of PD catheter removal - Samples were fixed with formalin and embedded in paraffin		205 [78 patients used acidic PD solutions & 127 patients used only neutral solution without history of treatment with acidic solution] • Short-term samples: • Long-term samples (treated for 4-10 years): 33 patients in each group	pH-neutral PD solutions	Acidic PD solution		**RESULTS** General -PD duration in the conventional group was significantly longer than in pH-neutral group (102; 95% CI 75.0, 132.0) months versus 44 (19.0, 72.0) months, respectively; $p < 0.001$) -Patients in conventional group had significant different compare with pH-neutral group in • Age: younger; $p < 0.001$ • Diabetes rate: lower rate of diabetes; $p < 0.001$ • Less use of Icodextrin; $p = 0.007$ • Included more patients treated with peritoneal lavage; $p = 0.02$ -Peritonitis incidence: very low in both groups → suggesting peritoneal membranes were not affected with peritonitis -No significant difference in dialysate-to-plasma ratio of creatinine (D/P Cre as a measure of peritoneal membrane function between the 2 groups; $p = 0.443$ Pathological Characteristics a. Thickness of peritoneal membrane • Thickness of peritoneal sub-mesothelial compact zone in the conventional group was significantly greater than in the pH-neutral group; 375.0; 95% CI 274.06, 602.00 vs 244.0; 95% CI 154.68, 390.25; $p < 0.001$ (table 2) • Long-Term: ○ D/P Cre in conventional group (0.70 ± 0.14) was significantly higher than in pH-neutral group (0.61 ± 0.12, $p = 0.008$) ○ Peritoneal thickness: Conventional group higher than pH-neutral group	Vasculopathy = ratio of luminal diameter /vessel diameter of post capillary venules with an external diameter of 25-50μm

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	Morphological Analysis - Samples collected at the time of catheter removal were assessed to evaluate the appropriateness of the sample size and sites and their potential inadequacy due to tissue damage - Things to evaluate: • Peritoneal thickness – the submesothelial compact zone was identified and the average value of the thickness at 5 points was calculated • Vasculopathy – the ratio of luminal diameter vessel diameter (L/V ratio) of post capillary venules with an external diameter of 25-50μm was assessed						p < 0.05 b. Vasculopathy (L/V ratio) • L/V ratio in conventional group; 0.50 ± 0.17, was significantly lower than that in the pH-neutral group; 0.76 ± 0.06, p < 0.001 ▪ The formation of new membrane and fibrin deposition was higher in conventional group than in pH-neutral group ▪ Number of CD31 positive vessels and CD68 positive cells were not significantly different between both groups • Long-term ○ L/Vratio : Conventional group higher than pH-neutral group p < 0.001 ▪ AGE score: Conventional group higher than pH-neutral group p < 0.001 ▪ CD31-positive vessels and CD68-positive cells were not significantly different between the two groups (p = 0.302 and p = 0.612, respectively) Relationship between PD duration and pathological changes -No correlation between peritoneal thickness and PD duration in both groups -L/V ratio decreased significantly over time in conventional group (r = -0.359, p = 0.008) -Vasculopathy did not progress over time in the pH-neutral group -CD31-positive vessels did not correlate significantly with PD duration in both groups Relationship between peritoneal function and pathological changes - To assess the correlations between peritoneal permeability (D/P Cre) and	

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							pathological changes → data used were on D/P Cre assessed within 1 year before catheter removal -D/P Cre correlated negatively with L/V ratio (r = -0.832, p = 0.037) in the conventional group and not related in neutral-pH group -Neither peritoneal thickness nor number of CD31 positive vessels correlated with D/P Cre Risk Factors for Pathological Changes -By multivariate analysis, conventional acidic PD solution and diabetes mellitus were identified as risk factors for peritoneal thickening (> 350 µm, HR 6.56, p < 0.001) -Conventional acids=c PD solution associated with vasculopathy (L/V ratio < 0.7, HR 18.3; p < 0.001) -Factors associated with an increase in CD31-positive vessels was not identified Conclusion pH-neutral PD solution can reduce the peritoneal morphological and functional deterioration resulting from long-term PD treatment	

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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
6. Chen JB, Cheng BC, Liu WH, Liao SC, Fu MYM, Moi SH & CH. Longitudinal Analysis of Cardiac Structure and Function in Incident-Automated Peritoneal Dialysis; Comparison Between Icodextrin Solution and Glucose-Based Solution. BMC Nephrol. 2018;19(1) :109. doi:0.1186/s12882-018-0912-7.	RCT Obj: to evaluate the longitudinal changes in cardiac structure and function in incident automated PD (APD) patients Methods: - Started in June 2005 and completed in May 2015 - Setting: patients were selected from PD unit in Kaohsiung Chang Gung Memorial Hospital, Taiwan - Cardiac structure and function were examined on echocardiography at baseline and subsequently in 1-year intervals - Purposive sampling method to enroll study participants in the outpatient department - Computer-generated block randomization method to categorized enrolled patient into 2 groups (ICO and GLU group) Monitoring & Assessment - Patients were requested to visit the PD outpatient clinic at least once every month and by telephone at		43 patients enrolled (21 in ICO group and 22 in GLU group) Inclusion criteria: - Adult incident-PD patients who agreed to receive nocturnal APD regimen with daily dwell - All participants underwent nocturnal APD with varying concentration of glucose-based PD solution - Age >18 years - New incident stage 5 CKD patients who agreed to receive renal replacement therapy with APD regimen and tolerate a long-dwell time of ≥ 10 hrs with 7.5% ICO solution ICO group - Participants received long-dwell exchange for 10-12 hrs with 7.5% ICO PD solution in daytime GLU group - Participants received 1 or 2 exchanges with glucose-based PD solution in daytime	7.5% Icodextrin PD solution	Glucose-based PD solution	Study duration 2 years	-Out of 43 participants 38 completed the study (20 in ICO group and 18 in GLU group) -Males predominant in ICO group and female predominant in GLU group -Diabetic nephropathy more prevalent in ICO group -Baseline levels of Hb, Cr, cholesterol, daily ultrafiltration amount and weekly renal Kt/V significantly differed between the 2 groups Left Ventricular End-Systolic Dimension (LVESD) -Compared with ICO group, the GLU group showed significantly lower baseline LVESD (35.00mm vs 30.49mm) Left Ventricular End-Systolic Volume (LVSEV) -Compared with ICO group, the GLU group showed significantly lower baseline LVSEV (53.48mm^3 vs 39.00mm^3) Cardiac Structure Measurements (from baseline to 24 months) •ICO group -LAD significantly increased -LVEDV, LVSEV, IVS significantly decreased -In LV diastolic function measurement, only septal EMV showed significant increase from baseline to 24 months (5.43 – 5.51ms) •GLU group -LAD, LVEDD, LVESD, LVEDV and LVESD all significantly increased -In LV systolic function measurement,	

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	least once a week - Data were collected from PD home record, including body weight, blood pressure level, ultrafiltration, amount and concentration of PD solution - Laboratory data including hemogram and biochemistry results were examined at baseline and monthly - Standard peritoneal equilibrium test (PET) was performed 1 month after APD commencement - Echocardiographic examinations - Cardiac performance was evaluated using pulsed Doppler echocardiography						only LVEF had a significant increase -Significant decreased in peak EDV (70.67 – 68.25cm/s) nut significant increase in septal EMV (5.94-7.57 ms) from baseline to 24 months (Table 4) General linear regression model -Foe association of clinical variables at base line with changes in echocardiographic parameters at 24 months from baseline -No significant model was found in present study -Multivariate models used to investigate changes in 4 primary end points (MPI, LVEF, DT and Ele' ratio) – table 5 -No significant association with the baseline values in both ICO and GLU groups Conclusion -No major differences in cardiac structure and function in both ICO and GLU solutions in incidence-APD → further research with bigger samples size required	

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7. Sikaneta T, Wu G, Abdolell M, Ng A, Mahdavi S, Svendrovski a, Tu T et al. The Trio Trial – A Randomised Controlled Clinical Trial Evaluating the Effect of a Biocompatible Peritoneal Dialysis Solution on Residual Renal Function. Pert Dial. Int: in Press. 2016;36(5):526-32. doi:10.3747/pdi.2015.00090	Obj: To examined the effect of biocompatible PD solution (Gambrosol Trio) with lower concentrations of glucose degradation products on rates of decline in RRF Methods - Sample size calculations to achieve 80% power to detect a difference iin slope of RRF of 0.15mL/min/1.73m2/month: 49 patients at least in each arms with drop-out rate allowed 20% - Group sampling by computerized algorithm - Treatment allocation: only treating nephrologist blinded Monitoring: - 24 hr urine specimens to calculate urea and creatinine clearances → collected every weeks for primary outcome assessment and to minimize impact of any inadvertent extracellular fluid volume depletion that may have had on RRF and urine volume Statistical Analysis		303 patients screened from August 2005 until July 2010 - 101 patients completed ≥ 3 GFR determinations for primary outcome analysis (51 Gambrosol group and 50 Dianeal group) Subjects recruitment - Subject were recruited from pre-dialysis outpatient clinics at Scarborough Hospital, Ontario and Princess Margaret Hospital in Hong Kong - Included criteria: • Patients were new to any renal replacement therapy • > 18 years' old • Urine volume > 100ml/day with GFRs of at least 1mL/min/1.73m^2	Biocompatible PD solution (Gambrosol Trio)	Standard PD solution [Low glucose concentration (Dianeal)]	2 years follow-up	**RESULTS** - 31 patients in Gambrosol group and 36 in Dianel group completed 2 years' follow-up Residual Renal Function - RRF declined by 0.132 ml/min/1.73m^2/month in Gambrosol group and 0.174 ml/min/1.73m^2/month in Dianeal group; significant p = 0.001 - Rates of decline were lower in biocompatible group regardless of initial RRF or starting PD modality Urine Output - Urine volume declined by 30ml/month in Gambrosol group and 39ml/month in Dianel group; p = 0.003 - Oligoanuria less frequently in biocompatible group; p = 0.001 - Time to anuria was not calculated as 4 of 9 patients with daily urine volumes under 100ml produced > 100ml on subsequent collections - Mean furosemide used was similar between groups at baseline (63 [38-89]mg/day in Gambrosol group and 55 [38 – 73]mg/dy in Dianel group; p = 0.60) - During the study the furosemide used was increased, mean 87 979-95) mg/day in Gambrosol group and 98 (91-106) mg/day in Dianel group; p = 0.036 Bioimpedence and Nutrition Indices - Body mass indices rose by 0.89 in biocompatible solution and 0.62 in Dianel groups a 1 year; p = 0.003 - Serum albumin and SGA scores did not differ between group - Mean protein catabolic rates: normalized	

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	-						for nitrogen appearance declined by 0.04 in the Dianel group and rose by 0.02 in Gambrosol group; p = 0.023 after 1 year - Serum phosphate level: lower (1.57 vs 1.64 mmol/L; p = 0.018) after 1 year in Gambrosol group - Plasma sodium level: higher (138 vs 137 mmol/l; p = 0.003) after 1 year in Gambrosol group - No difference in total water stores between groups - Fat mass rose more in Ganbrosol group (2.8% vs 1.7% per year; p = 0.046) Peritoneal Dialysis and Membrane characteristics - Peritoneal ultrafiltration volume increased and D/P creatinine decreased during the study, but no difference between groups - Peritoneal Kt/V declined (p = 0.042) while urine Kt/V increased (p = 0.029) in biocompatible group over study period - Urine weekly creatinine clearances declined at slower rate in biocompatible arm (p = 0.024) while peritoneal weekly creatinine clearances did not differ between groups Icodextrin and Automated Cycler Use - Icodextrin was prescribed in 3 of 29 (10.3%) vs 13 of 33 (39%) of Canadians patients; p = 0.01) - Icodextrin use was associated with faster declines in RRF (0.193 vs 0.149 ml/min/1.73m^3/month [p = 0.04] and urine volumes (40 vs 24ml/month [p = 0.001]→ In fixed effects PD solution had no significant effect on RRF (p = 0.198) and urine volume (p = 0.112) - RRF and urine volume still decline at slower rates n 46 Canadian patients	

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							who did not receive Icodextrin is allocated to the Gambrosol Group (0.113 vs 0.162 ml/min/1.73m3/month [p = 0.013] and 16 vs 27 ml/month [p = 0.006]) - 32 (52%) Canadian patients were prescribed an automated cycler at some point in the study → 11 in Gambrosol group and 21 in Dianeal group (p = 0.043) • Automated cycler did not significantly associate with RRF Peritonitis Rate - Significantly higher in Gambrosol group - Not associated with initial PD prescription or subsequent PD modality changes and did not change the finding of slower RRF decline rates in patients treated with biocompatible solution - C-reactive protein levels did not differ between group Adverse Events - No differences between groups in the numer of death (2 in each groups) or hospitalization (24 [54%] in Gambrosol group and 21 [46%] in Dianel Groups; p = 0.48) Survival Analysis - No difference between group in peritoneal technique survival rates (p = 0.13) - Cox proportional regression analysis showed: survival to be negatively affected by: • Peritonitis events (HR 1.60 (95% CI 1.00, 2.56) • Heart failure (HR 3.85, (95% CI 1.13, 13.17) • Use of an automated cycler (HR 6.06 (95% Ci 1.42, 25.74)	

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							Conclusion - Incident PD patients treated with the biocompatible PD solution Gambrosol Trio had slower rates of decline in RRF ✓ Associated with better-preserved urine volumes, ✓ Less Icodextrin and Automated cycler use, and ✓ More favourable serum phosphate and nutrition profiles. - However, use of Gambrosol Trio was also associated with ✓ Higher rates of peritonitis → requires further investigation and precaution before wider-spread use of Gambrosol Trio can be recommended	

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8. Han SH, Ahn SV, Yun JY, Trannaeus A & Han DS. Effects of Icodextrin on Patient Survival and Technique Success in Patients Undergoing Peritoneal Dialysis. Nephrol Dial Transplant. 2012; 27: 2044-2050	Retrospective cohort Obj: To investigate whether Icodextrin solution use may confer patient and technique survival advantages in PD patients Materials and Method - Inclusion: 2311 incident ESRD patients from 54 PD centers in Korea who commenced PD using Baxter solutions between July 2003 and December 2006 → 148 excluded → included in final analysis 2163 - Data were retrospectively collected: demographic, clinical and outcome data (age, gender, underlying renal disease, cardiovascular comorbidity, residual urine output, and types of PD solution at initiation of PD, duration of Icodextrin used, follow-up duration, reason for drop out and cause of death Statistical Analysis - Post-hoc analysis using Baxter Korea Database		2,163	pH neutral (Physioneal) (bicarbonate/lactate-buffered PD solution	Dianel (conventional)		**RESULTS** Patient Characteristics and Comparison of Baseline Covariates - Mean age at the start of PD was 54.9 ± 13.6 years and 53.3% were male - Mean follow-up duration of PD was 23.7 ± 12.4 months with a range of 3.1 – 50.3 months - 641 patients met the criterion for the Icodextrin group, and the other 1522 were categorized as non-Icodextrin group - Mean duration of Icodextrin used: 18.0 ± 9.3 (2.0 – 46.4) months (average 75.8% of total PD duration in the former and 2.0 ± 4.2 (0 – 23.3) months (average 7.8% of total PD duration) in the latter ($p < 0.001$) - In non-Icodextrin group, 907 (59.6%) patients never used Icodextrin solution and remaining 615 patients used Icodextrin at least 1 day - Significant differences in underlying renal disease, B/L solution and SES in both groups - Compared with non-Icodextrin group, more patients with diabetes (63.7% vs 48.7%, $p < 0.001$), low SES (32.3% vs 23.4%, $p < 0.01$) and used of B/L solution (32.1% vs 22.1%, $p < 0.001$) in the Icodextrin group - The unbalance condition at baseline between both groups were controlled by using PS matching (propensity score) → after PS matching, 74 patients (5.8%) treated with APD, 45 patients (7.0%) in the Icodextrin groups and 29 patients (4.5%) in the non-Icodextrin group but not statistically significant Patients Outcome - Mortality	

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							- In the matched cohort, all-cause deaths occurred in 92 (14.4%) patients in the Icodextrin group compared with 128 (20.0%) in the non-Icodextrin group (p = 0.006) - Kaplan-Meier plot: all-cause mortality was significantly lower in patients using the Icodextrin solution (p = 0.004) - 2 and 4-year patient mortality rates were 14.2% and 26.4% in the Icodextrin group and 20.0% (p = 0.004) and 31.1% (p = 0.004) in non-Icodextrin group - Multivariate Cox analysis: adjusted for age, gender, diabetes, cardiovascular comorbidity, types of PDS (B/L or conventional), SES and center experience, Icodextrin use was associated with a significantly lower risk of death (HR 0.69; 95% CI 0.53, 0.90; p = 0.006) - There were some patients used both solutions, so Cox proportional hazard model was tested for any interaction between both solution: no significant interaction was observed between the 2 solutions (p = 0.520) - Sensitivity analysis: • 804 patients (data on residual urine output available) • No significant difference in residual urine output at initiation of PD between the 2 matched groups (608.5 ± 418.4 ml/day in Icodextrin group [n = 381] versus 612.3 ± 414.9 ml/day in non-Icodextrin group [n = 423], p = 0.898) • After adjustment residual urine output, survival benefit of Icodextrin remained significant (HR = 0.63; 95% CI 0.45, 0.90; p = 0.011) - Cause of death (overall no difference in cause of death between 2 matched group)	

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							• Cardiovascular death: 64.8% (although CVS mortality was lower in Icodextrin patients, but not significant p = 0.072) (in multivariate Cox analysis: Icodextrin was associated with tendency towards decreased risk of cvs mortality although not significant; HR 0.76; 95% CI 0.54, 1.05,, p = 0.098) • Infectious death: 24.6% (no difference in both solution group, p = 0.204) • Advanced liver disease: 1.8% • Malignancy: 1.4% • Malnutrition: 0.9% • Others (not mentioned): 6.5% Patients Outcomes: Technique Failure - Technique failure occurred in 36 (5.6%) patients in Icodextrin group compared with 56 (8.8%) in non-Icodextrin group; p = 0.030) - Kaplan Meier plot: compared with non-Icodextrin group, technique failure rate was significantly lower in patients using Icodextrin solution (p = 0.018) - Multivariate Cox analysis: Icodextrin used was significantly associated with a decreased risk of technique failure (HR 0.60; 95% Ci 0.40-0.92; p = 0.018) - Causes of technique failure: • Peritonitis (46.7%) – no difference in both group • Non-compliance: (Icodextrin group had significantly lower technique failure than non-Icodextrin group; 0.6% vs 2.0%; p = 0.048) • UF – no difference in both group Conclusion: may do RCT or prospective trial	

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Question: Is it BIOCOMPATIBLE PD SOLUTION effective for peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
9. Stankovic-Popovic A, Nesic V, Popovic D, Maksic D, Coliv M et al. Effects of conventional versus biocompatible peritoneal dialysis solutions on peritoneal and systemic inflammation, malnutrition and atherosclerosis (MIA) in CAPD patients. Clin Nephrol. 2011; 76(4): 314-322	Cross-sectional (single-centre) Obj: to evaluate the effects of PD solutions (standard vs biocompatible) on some parameters of MIA syndrome in patients undergoing CAPD Methods: - No significant differences in prescription of statins, aspirin, erythropoietin, vitamin D metabolites and iron between groups from start of CPAD until the time of analysis Setting: Military Medical Academy Belgrade where patients were treated by CAPD according to mode of insurance Analysis: - RRF was estimated by calculating the mean of renal clearances of urea and creatinine from 24 hrs urine collection (GFR – ml/min) and by measuring serum level of cystatin C by particle-enhanced nephelometric immunoassay		42 CAPD patients (26 men and 16 female) Patients were analysed and grouped according to type of insurance (CAPDP-1 & CAPDP-2 group) Included criteria - Who had at least 2.5 years of treatment at the time of analysis Excluded criteria - Patient with severe anemia (Hb <10 g/l) - Patients on immunomodulatory therapy - With peritonitis or any inflammatory conditions for at least 3 months before analysis - Malignant disease - Acute exacerbation of heart failure	Biocompatible PD solution – lower level of glucose degradation products (GDPs), lower concentration calcium and neutral pH CAPD-2 group (covered by military insurance) - 1 patients (50%)	Bio-**in**compatible PD solution – conventional glucose-based, lactate buffered solutions CAPD-1 group (patients with civil insurance) - 1 patients (50%)		**RESULTS** - Selection bias: avoided since there was no significant differences between the groups in age, gender, underlying renal disease and baseline residual renal function, ultrafiltration and peritoneal transport characteristics - No differences between groups in comorbidity and previous medication (including erythropoietin-stimulating agents, ACE inhibitors, iron and vitamin D metabolites, social status and monthly income - After 3.1 ± 0.4 year for CAPDP-1 and 3.5 ± 0.5 year for CAPDP-2 group, the inflammatory markers in serum and peritoneal effluent were analyzed a. Mean value of serum hs-CRP: significantly lower in CAPDP-2 group than in CAPDP-1 group b. Serum ferritin and fibrinogen: no significant differences between groups c. Serum and effluent level of IL-1, IL-6 and TNF-α and in CA-125 effluent level: no difference in both group d. Total serum cholesterol, triglycerides, bicarbonates, albumin and BMI: no significant differences between groups e. Mid-arm circumference, mid-arm muscle circumference and SGA: patients in CAPDP-1 group had significantly worst nutritional status than patients in CAPDP-2 group f. Peritonitis incidence: not confirm significant difference (0.27 ± 0.33 episodes/year for CAPDP-1 group and 0.33 + 0.40 episodes/year for CAPDP-2 group) g. Cardiovascular score: • Mean ejection fraction (EF): no	

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							difference in both group • Frequency of vulvular calcification: higher frequency in CAPDP-1 but not significance • Significant differences between groups were observed in: prevalence of left ventricular hypertrophy (LVH), CVS, IMT, degree of carotid narrowing and calcified plaques of CCA - Logistic regression analysis: biocompatibility of PD solutions was not confirmed as an independent risk factor for any parameter of malnutrition, inflammation and atherosclerosis Conclusion - Require further well-designed and controlled studies in larger numbers	

Evidence Table: Efficacy/Effectiveness
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10. Davies SJ, Brown EA, Frandsen NE et al. Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and Icodextrin prescription. Kidney international. 2005 Apr 1;67(4):1609-1615.	Prospective Cohort Aim: To establish the efficacy of this treatment modality in functionally anuric patients treated according to previously agreed targets for anemia, several biochemical variables, small solute clearance, and daily ultrafiltration and to examine the effects of dialysis prescription on any possible changes without the confounding effect of residual renal function. Methods: - The design and analysis of primary endpoints (patient and technique survival) of EAPOS are described in detail elsewhere. Briefly, it was a prospective study of functionally anuric patients (urine volume <100 mL and/or creatinine clearance <1 mL/min/1.73m2) treated with APD undertaken in 28 centers in 14 European countries. One hundred seventy-seven of 204 screened patients were enrolled and followed for two	II-2	177 patients treated with APD enrolled into European Automated Peritoneal Dialysis Outcomes Study (EAPOS) Briefly, 57% were men, median age was 54 (range 21–91) and 80% were Caucasian, 12% Indo-Asian. Low glucose exposure was defined as regimens containing 1.36% only, used by 43 (24%) of patients, whereas 134 patients used at least one 2.27% or 3.86% exchange. Just under half 82 (46%) of patients were using Icodextrin at baseline.	Icodextrin	No Icodextrin	Up to 24 months	**RESULTS** No changes for Icodextrin group in ultrafitration capacity and relatively small but significant increase in solute transport, but still less value as compared to no Icodextrin group. **Mean Solute transport** **Using Icodextrin**: no different from baseline to 24 months Baseline: Mean (SD) 0.76 (0.11) 12 months: 0.79 (0.11) 24 months: 0.78 (0.1) **No Icodextrin**: increase from baseline to 24 months Baseline: Mean (SD) 0.74 (0.11) 12 months: 0.83 (0.1) 24 months: 0.85 (0.1) **Low Glucose**: increase from baseline to 24 months (not significant) Baseline: Mean (SD) 0.74 (0.11) 12 months: 0.76 (0.08) 24 months: 0.8 (0.11) **High Glucose**: increase from baseline to 24 months (significant) Baseline: Mean (SD) 0.75 (0.12) 12 months: 0.8 (0.11) 24 months: 0.82 (0.1) **Ultrafiltration capacity** **Using Icodextrin:** increase capacity from baseline to 24 months Baseline: Mean (SD) 272 (302) 12 months: 277 (312) 24 months: 299 (292) **No Icodextrin:** decrease from baseline	

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	years, or until they stopped peritoneal dialysis. Clinicians were asked to optimize treatment to predefined standards during the first six months, including a solute clearance target of ≥60l/week/1.73m2, and a daily ultrafiltration volume of ≥750 mL. Clinicians had access to Icodextrin, used according to clinical discretion, and standard, pH 5.5, 40 mmol lactate-buffered glucose solutions						to 24 months Baseline: Mean (SD) 374 (232) 6months: 318 (228) 12 months: 188 (264) **Low Glucose**: decrease from baseline to 24 months (not significant) Baseline: Mean (SD) 309 (278) 12 months: 318 (279) 24 months: 276 (250) **High Glucose**: decrease from baseline to 24 months (significant) Baseline: Mean (SD) 333 (269) 12 months: 293 (271) 24 months: 228 (290) **Peritonitis Rate** No statistically significant between for all groups **Conclusion** One of the important findings of EAPOS was a modest but highly significant fall in achieved ultrafiltration during the course of the study that cannot be explained by informative censoring, reduced use of hypertonic glucose, or Icodextrin	

SAFETY

Evidence Table: Safety
Question: Is it BIOCOMPATIBLE PD SOLUTION safe to be used in peritoneal dialysis?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow-up (if applicable)	Outcome measures/ Effect size	General comments
11. Htay H, Johnson DW, Wiggins KJ, Badve SV, Craig JC, Strippoli GFm and Cho Y. Biocompatible Dialysis Fluids for Peritoneal Dialysis. Cochrane Database of Systematic Reviews. 2018; Issue 10. Doi: 10.1002/14651858	SR with MA Objective: To look at the benefits and harms of biocompatible PD solutions in comparison to standard PD solutions in patients receiving PD Methods: Data collection and analysis • 2 authors involved • Summary effects using random-effects model • Results were expressed as risk ratios and 95% CI for categorical variables and MD or SMD and 95% CI for continuous variables Outcome • Toxicity/adverse events (rahs, uncontrolled fluid overload etc)		Selection Criteria: • All RCTs and quasi-RCTs in adults and children comparing the effects of biocompatible PD solutions in PD were included 42 eligible studies included (3262 participants • 6 new studies (543 participants • 29 studies (1971 participants) compared neutral pH, low GDP, PD solutions with conventional PD • 13 studies (1291 participants) compared Icodextrin with conventional PD	Biocompatible PD solutions Neutral PH, lactate buffered, low-GDP Neutral pH, bicarbonate (± lactate)-buffered, low GDP Glucose polymer (Icodextrin)	Conventional glucose PD solutions		**RESULTS** Adverse Event - In low certainty evidence, Icodextrin may make little or no difference to the risk of rash compared with glucose exchanges (3 studies, 755 participants): RR 2.51, 95%CI 0.59 to 10.72; I^2 = 38%) - In very certainty evidence, it is uncertain whether Icodextrin use led to any differences in adverse events (5 studies, 816 participants) (Lin 2009a; MIDAS 1994; Paniagua 2008; STARCH 2015; Wolfson 2002)	

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12. Sikaneta T, Wu G, Abdolell M, Ng A, Mahdavi S, Svendrovski a, Tu T et al. The Trio Trial – A Randomised Controlled Clinical Trial Evaluating the Effect of a Biocompatible Peritoneal Dialysis Solution on Residual Renal Function. Pert Dial. Int: in Press. 2016;36(5):526-32. doi:10.3747/pdi.2015.00090	Obj: To examined the effect of biocompatible PD solution (Gambrosol Trio) with lower concentrations of glucose degradation products on rates of decline in RRF Methods - Sample size calculations to achieve 80% power to detect a difference iin slope of RRF of 0.15mL/min/1.73m2/month: 49 patients at least in each arms with drop-out rate allowed 20% - Group sampling by computerized algorithm - Treatment allocation: only treating nephrologist blinded		303 patients screened from August 2005 until July 2010 - 101 patients completed ≥ 3 GFR determinations for primary outcome analysis (51 Gambrosol group and 50 Dianeal group) Subjects recruitment - Subject were recruited from pre-dialysis outpatient clinics at Scarborough Hospital, Ontario and Princess Margaret Hospital in Hong Kong - Included criteria: • Patients were new to any renal replacement therapy • > 18 years' old • Urine volume > 100ml/day with GFRs of at least 1mL/min/1.73m^2	Biocompatible PD solution (Gambrosol Trio)	Standard PD solution [Low glucose concentration (Dianeal)]	2 years follow-up	**RESULTS** Adverse Events - No differences between groups in the numer of death (2 in each groups) or hospitalization (24 [54%] in Gambrosol group and 21 [46%] in Dianel Groups; p = 0.48)	