Peritonitis

Dr Nader Nourimajalan

Peritonitis

- Peritonitis continues to be a major cause of morbidity and mortality in PD patients globally

Depending on the underlying organism, peritonitis is complicated by

- Relapse in 3%–20% (14% overall),
- Catheter removal in 10%–88% (22% overall),
- Permanent HD transfer in 9%–74% (18% overall),
- Death in 0.9%–8.6% (2%–6% overall) of cases,

Peritonitis

- Severe and/or repeated peritonitis episodes may also culminate in sufficient damage that precludes successful PD and, rarely, encapsulating peritoneal sclerosis.

- Imposes a heavy financial burden on the health care system the average cost of $3100.

- PD peritonitis represents one of the most important patient-related barriers to the greater uptake of PD.

Peritonitis deteriorate solute transfer and ultrafiltration

- In addition to chronic inflammation, episodes of peritonitis resulting in higher solute transfer rates and lower ultrafiltration.

- Locally released nitric oxide, may mediate it.

- Pharmacologic inhibition or genetic deletion of nitric oxide synthase significantly attenuates inflammation and changes in ultrafiltration.

The impact of peritoneal dialysis-related peritonitis on mortality in peritoneal dialysis patients

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1321 patients

- Peritonitis was independently associated with
- 95% increased risk of all-cause mortality
- 90% increased risk of cardiovascular mortality
- 4-fold increased risk of infection-related mortality

Peritonitis

- Peritonitis is a preventable condition, infection rates around the world have decreased considerably over time.
- The rates of PD-related infections have steadily decreased over the last 10–20 years.
- Most apparent for Gram-positive infections, significant reductions have also been reported for Gram-negative peritonitis.

Peritonitis Rates

- These reductions have been attributed to the use of

  - Twin bag disconnection systems,
  - Implementation of mupirocin chemoprophylaxis protocols,
  - Topical exit site application of gentamicin, nystatin or fluconazole,
  - Improved training of PD patients and/or staff,
  - Better identification and targeting of peritonitis risk factors.

Peritonitis Rates

- There remains a wide and unacceptable variation in rates from different countries, ranging from 0.06 episodes/year in Taiwan to 1.66 in Israel,
- Up to 20-fold variation in peritonitis rates between centers within individual countries,
- Center-related factors, such as unit size, topical antibiotic prophylaxis, or PD training practices may affect it.
- Highly variable and generally poor compliance of centers with clinical practice guidelines for prevention of peritonitis.

Peritonitis taskforce

- Key strategies for correcting this ubiquitous problem in PD include benchmarking of PD center peritonitis rates and outcomes through
  - The establishment of national PD peritonitis registries within each country,
  - Alignment of PD practice in each center with clinical practice guidelines,
  - Strengthening of clinical governance within each unit, and
  - Adoption of a whole-of-unit approach to continuous quality improvement,
  - Root cause analysis of all cases of peritonitis within each center to identify areas for improvement.

Peritonitis should be diagnosed if two or more of following are present

- Consistent clinical features (abdominal pain or cloudy effluent).
- Peritoneal fluid white count is greater than 100 cells/mm^3 (or 0.1 x 10 9/L after dwell time of at least two hours) and the percentage of neutrophils is greater than 50 percent.
- Positive effluent culture.

Gram stain and culture

- Gram stain and culture — Peritoneal fluid culture is positive in approximately 80 to 95% of peritonitis cases
- The gram stain is usually negative; Gram stain may be particularly useful in the early diagnosis of fungal peritonitis.

- In up to 22% of cases, PD fluid cultures prove to be negative and thus the patient with culture-negative cloudy dialysate

These patients are referred to as having aseptic, culture negative, or sterile peritonitis.

Sterile peritonitis is a frequently occurring condition with a variety of causes.

- 45% of cases of sterile peritonitis were associated with technical difficulties in collecting a sample
- 26% other causes: It is helpful to classify sterile peritonitis by the PD effluent cell count

ü cellular

ü noncellular causes

Differential Diagnosis of Cloudy Effluent

- Culture-positive infectious peritonitis
- Infectious peritonitis with sterile cultures
- Chemical peritonitis
- Calcium channel blockers
- Eosinophilia of the effluent
- Hemoperitoneum
- Malignancy (rare)
- Chylous effluent (rare)
- Specimen taken from "dry" abdomen

DIFFERENTIAL DIAGNOSIS

Cloudy peritoneal effluent (culture negative)

- Multiple conditions may cause cloudy effluent.

Ø noncellular

Ø cellular

Differential Diagnosis of Sterile Peritonitis

- Cellular causes
  - Increased neutrophils
    - Atypical infection
      - Mycobacteria
      - Fungi
    - Intraperitoneal disease
      - Cholecystitis
      - Appendicitis
      - Small bowel incarceration
      - Mesenteric ischemia
      - Sterile abscess rupture
    - Retroperitoneal disease
      - Pancreatitis
      - Splenic infarction
      - Abscess
      - Renal cell carcinoma
    - Drugs
      - Amphotericin B
      - Vancomycin
    - Contamination of PD fluid
      - Endotoxin
      - Acetaldehyde
  - Increased eosinophils
    - Allergic reaction
      - Tubing
      - Bags
    - Intraperitoneal air
    - Drugs
      - Vancomycin
      - Gentamicin
      - Streptokinase
      - Cephalosporins
    - Following peritonitis
    - Infection
      - Fungal
      - Parasitic
    - Retrograde menstruation
  - Increased monocytes
    - Icodextrin related
    - Mycobacteria
    - In association with eosinophilia
  - Increased erythrocytes
    - Any cause of hemoperitoneum
    - Retrograde menstruation
    - Ovulation
    - Ovarian/hepatic cyst rupture
    - Peritoneal adhesions
    - Strenuous exercise
    - Catheter-associated trauma
  - Increased malignant cells
    - Lymphoma
    - Peritoneal metastases
      - Adenocarcinoma
- Noncellular causes
  - Increased fibrin
    - Post peritonitis
    - Starting PD
  - Increased triglycerides
    - Acute pancreatitis
    - Neoplasms
    - Catheter-associated trauma
    - Superior vena cava syndrome
    - Drugs
      - Calcium channel blockers

Chemical peritonitis

What are the GDPs

Glucose is known to degrade to carbonyl compounds during heat sterilization and during subsequent storage These are generally referred to as glucose degradation products (GDPs).

- Higher solution PH, higher temperature, and longer sterilization time during the manufacturing process result in increased production of GDP

Glucose degradation products identified in peritoneal dialysis solutions

GDP	Molecular weight *g/mol*	Concentration *μM*
Acetaldehyde	44.05	120–420
Formaldehyde	30.03	6–15
2-furaldehyde	96.08	0.05–2
Glyoxal	58.04	3–14
5-hydroxymethylfuraldehyde	126.1	6–30
Methylglyoxal	72.06	2–23
Valeraldehyde	86.13	n.d.
3-deoxyglucosone	162.14	118–154
3,4-dideoxyglucosone-3-ene	144.12	9–22

GDP is glucose degradation product.

Glucose degradation, a comprehensive scheme for mildly acidic conditions such as in peritoneal dialysis (PD) fluids

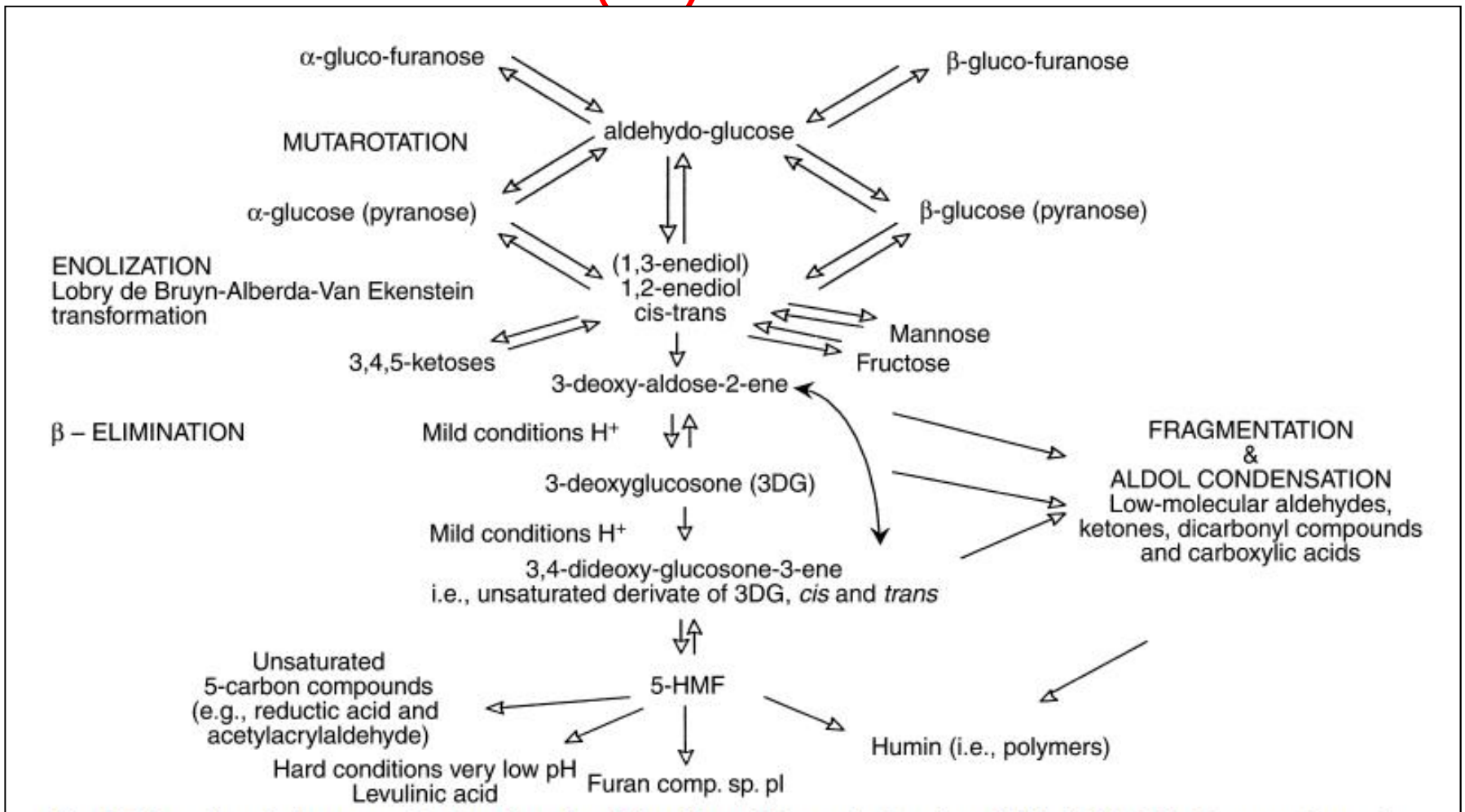


Fig. 1. Glucose degradation, a comprehensive scheme for mildly acidic conditions such as in peritoneal dialysis (PD) fluids. Fragmentation reactions on enols and dicarbonyl compounds produce low molecular aldehydes and carboxylic acids. Also, recombination of fragments and intermediates could occur. The number of possible degradation products is probably very high.

Reaction paths for the production of particles, gas and oil from decomposition of glucose under hydrothermal conditions.

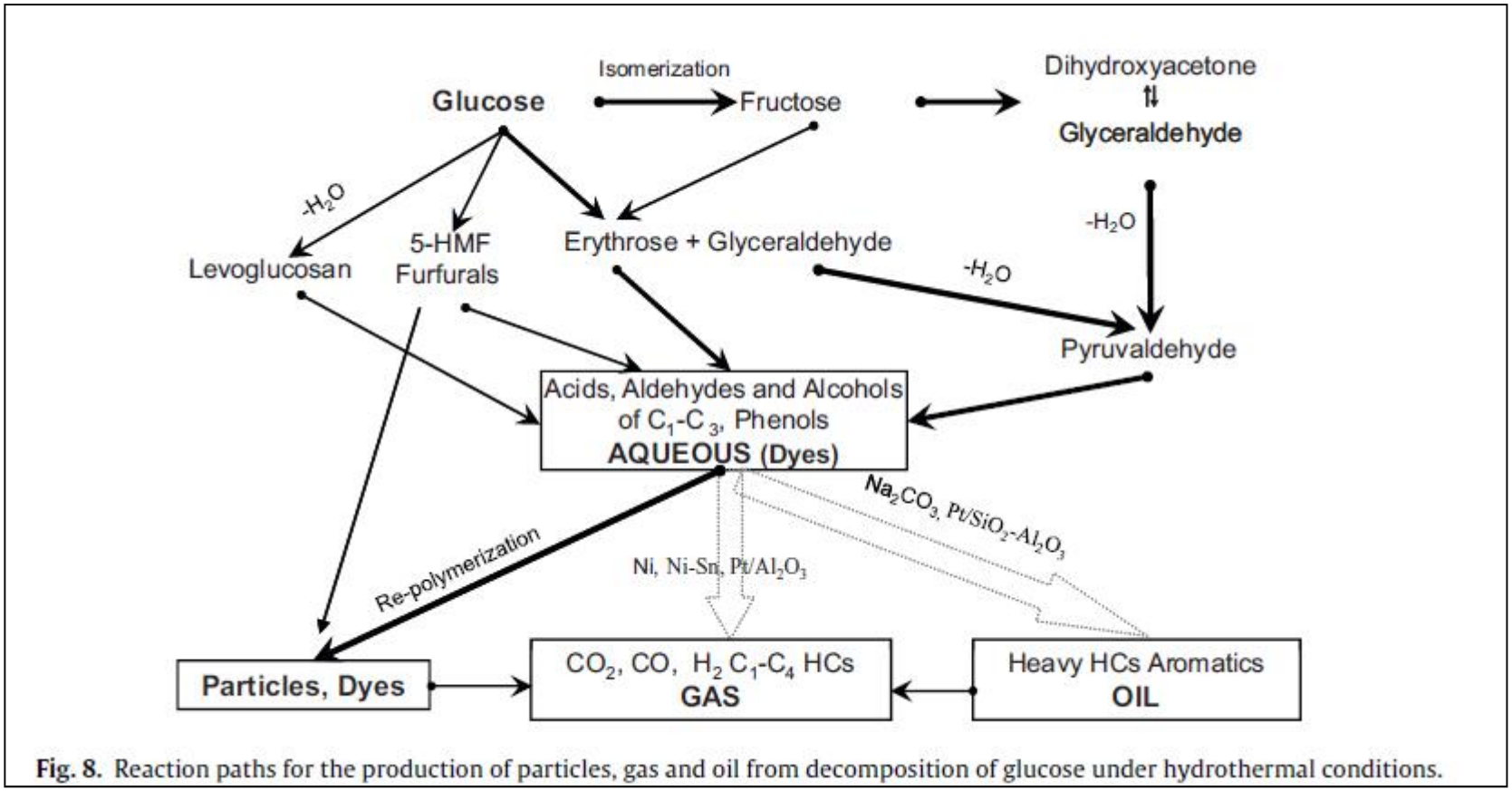


Fig. 8. Reaction paths for the production of particles, gas and oil from decomposition of glucose under hydrothermal conditions.

Main reaction pathway of glucose transformation in high-temperature steam.

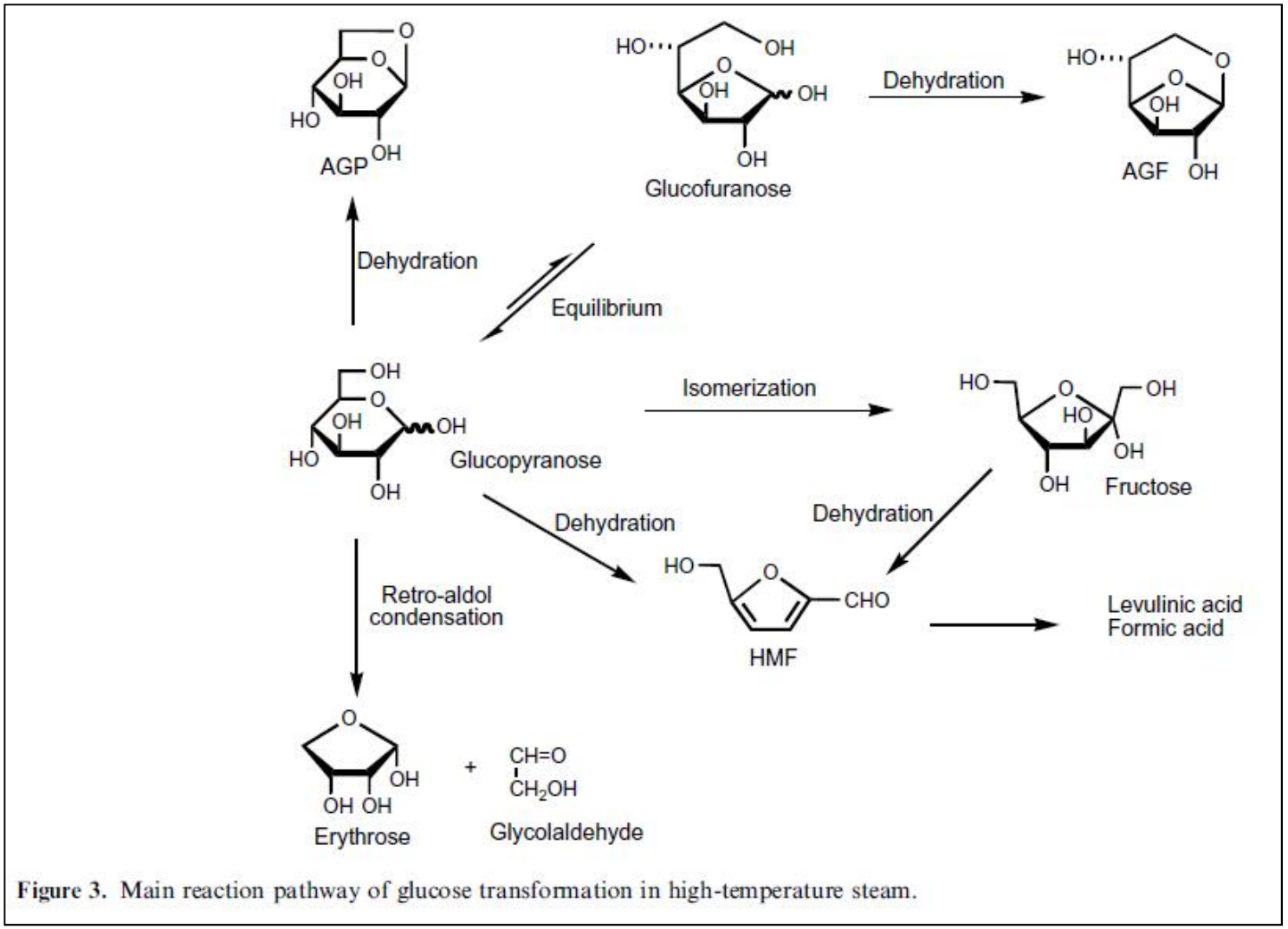


Figure 3. Main reaction pathway of glucose transformation in high-temperature steam.

Glucose Degradation Products (GDPs) (mmol/L) in 1.5% Peritoneal Dialysis Fluids Stored at 25°C or 40°C After Sterilization. At 25°C, equilibrium was reached after 30 days; 8 days was needed at 40°C.

Storage	0 days	25°C 8 days	25°C 30 days	40°C 8 days	40°C 30 days
3,4-DGE	125±4	64±3[a]	25±1[a]	39±2[a]	32±2[a]
3-DG	230±6	273±2[a]	307±7[a]	286±3[a]	265±12[a]
5-HMF	14±0	14±0	14±0	17±1[a]	21±1[a]
Methylglyoxal	1±1	1±1	1±1	1±1	3±1
Glyoxal	12±1	10±0	9±0[a]	10±0	9±0[a]
Formaldehyde	4±1	4±0	4±1	6±0	6±1[a]
Acetaldehyde	84±7	93±3	83±2	86±1	106±3[a]

3,4-DGE = 3,4-dideoxyglucosone-3-ene; 3-DG = 3-deoxyglucosone; 5-HMF = 5-hydroxymethyl furaldehyde.

[a] $p < 0.05$.

Statistical comparisons were made between the values of

An increase in incubation temperature resulted in an increase in the concentration of 3,4-DGE and cell Cytotoxicity

	5°C	25°C	30°C	40°C	60°C
3,4-DGE (μmol/L)	11±1	12±1	16±1	24±2	38±3
3,4-DGE after dilution (μmol/L)	7	8	10	16	26
ICG (%)	22±3	25±4	30±4	32±3	44±4

3,4-DGE = 3,4-dideoxyglucosone-3-ene; ICG = inhibition of cell growth.

3,4-DGE values are given as mean±SEM (n = 3); ICG values are given as mean±SEM (n = 6).

- Our results emphasize that patients should not use glucose-containing PD fluids too soon after sterilization. A quarantine period of at least 1 month at room temperature should be ensured before the patient uses the fluids.

Do GDPs harm?

Glucose degradation products (GDPs) in peritoneal dialysis (PD) fluids are cytotoxic and affect the survival of the peritoneal membrane.

- Acute side effect (chemical peritonitis)
- Chorionic side effect

Chorionic Side Effect

3,4-DGE is key substance for determining bio incompatibility of PD fluids.

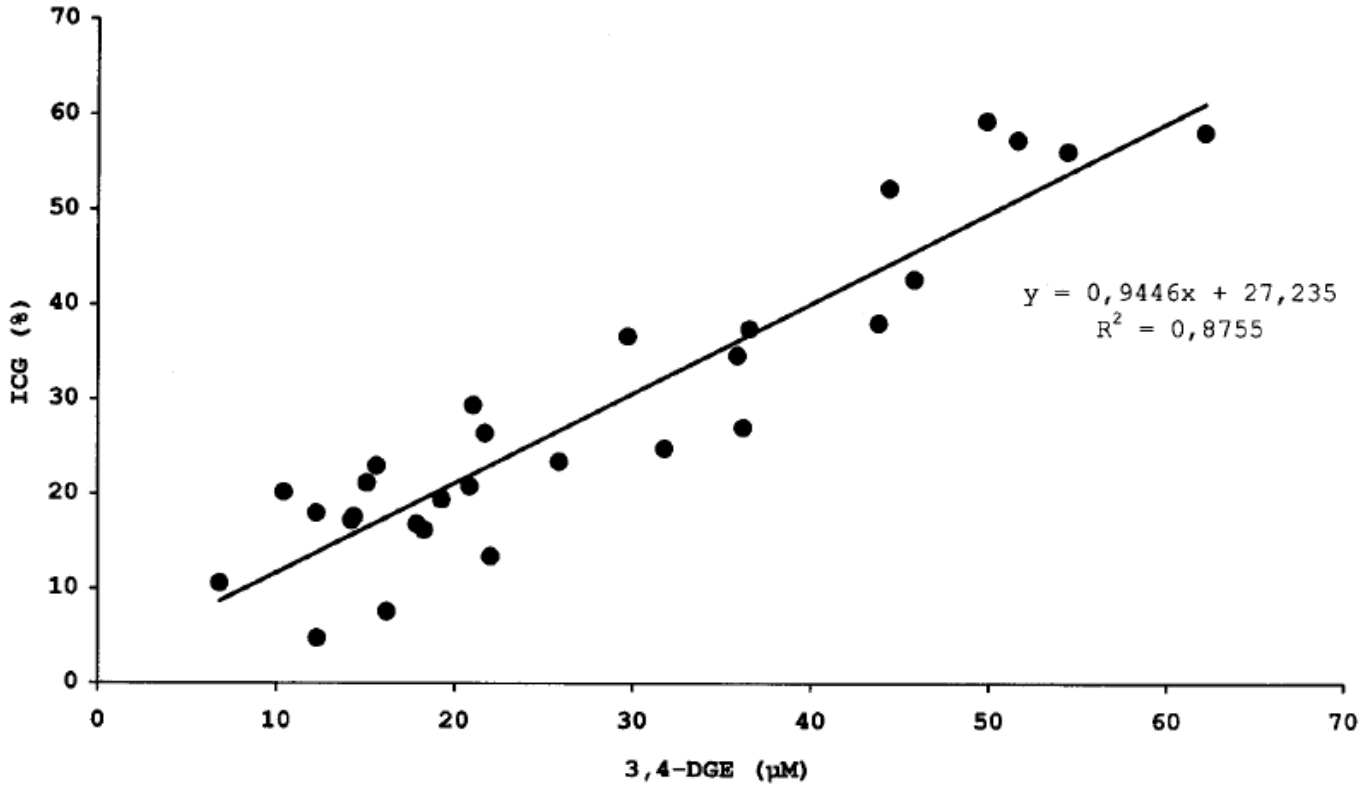
- 3,4-DGE is the only GDP that has adverse effect at the concentrations found in PD fluids. The concentrations of other GDPs tested have to be at least three times, and in most cases more than ten times, higher circumstances is than those actually found in the PD fluids in order to induce adverse effect.

Adverse effect of 3,4-DGE

- Cytotoxicity of mesothelial cell proliferation and function
- Suppresses immune cells/functions
- A promoter of AGE pressed formation

Ø By using new manufacturing procedures 3,4-DGE formation in fluids for PD may be almost totally avoided.

Correlation between 3,4-DGE concentrations Inhibition of cell growth (ICG),



- Immediately after sterilization, cytotoxicity of the PD fluids was high. It decreased in parallel with the decrease in 3,4-DGE concentrations.

Acute chemical peritonitis

Chemical peritonitis is rare but important causes of epidemics of peritonitis

1- Turkish: 21 cases (1996); NDT 2000

2- Iran: more than 150 cases (2000); Unpublished

3- Iran: 20 cases (2006); PDI 2008

4- India: 13 cases (2014); PDI 2016

5- Iran: more than 400 cases (2018); Unpublished

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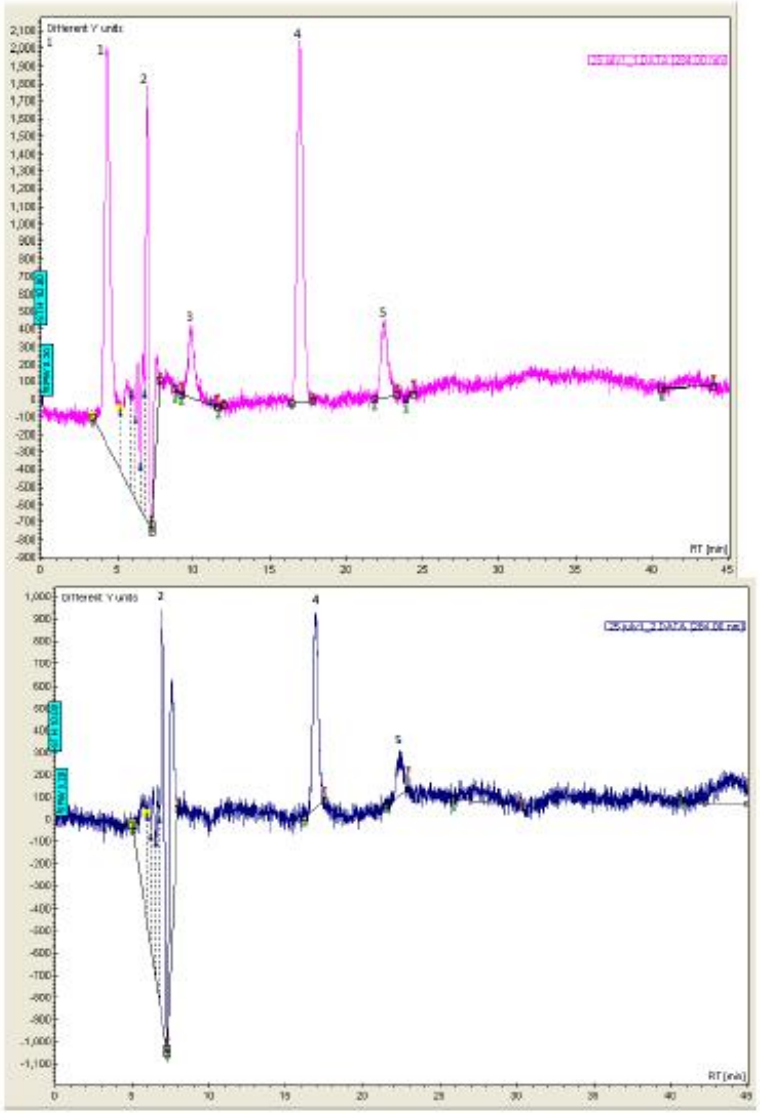
SHORT REPORTS

- **Epidemic of Chemical Peritonitis in Patients on Continuous Ambulatory Peritoneal Dialysis: A Report from Western India**

Dialysate was tested for presence of acetaldehyde by HPLC (Jasco, MD, USA) using a Spherisorb S5P column (Waters, MA, USA). Separation of acetaldehyde was performed using ammonium acetate (11.6 g/L, pH 4.0) as mobile phase with a flow rate of 0.45 mL/min and 25°C column temperature. Detec-

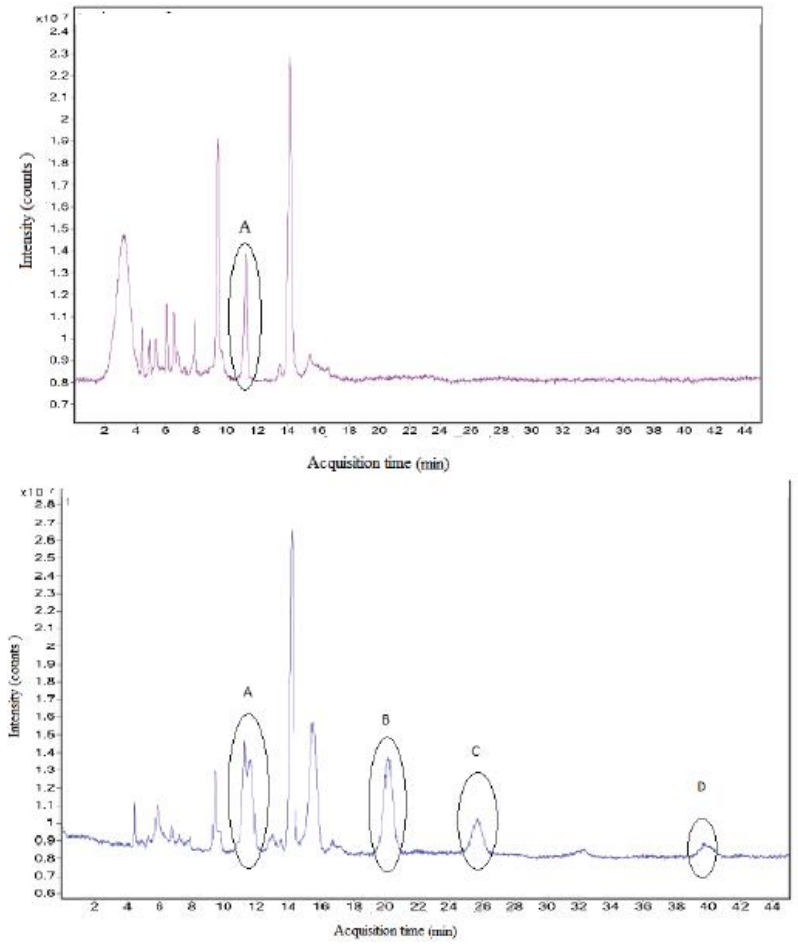
- From 15 April 2014 to 5 June 2014, 13 of 26 patients on peritoneal dialysis (PD) were evaluated for peritonitis.
- All 13 (100%) had cloudy effluent, 11/13 (76.47%) had abdominal pain, and 5/13 (38.4%) had systemic symptoms in the form of fever and chills.
- Median effluent cell count was 2,000 cells/mm3 (range: 260 – 10,000 cells/mm3) with 85% polymorphs
- The endotoxin level tested on the common suspect batch was < 0.25 EU/mL. Acetaldehyde was not detectable in the samples tested by HPLC analysis.

High pressure liquid chromatography analysis of suspect (top) and control (bottom) batches of fluid



- At absorption maxima of 284 nm, fluid A shows 5 peaks while fluid B shows 3 peaks, indicating the presence of additional entities in the suspect batch of peritoneal

Liquid chromatography mass spectrometry analysis of normal (top) and suspect (bottom) dialysate batches.



- GDPs with molecular weight of 90, 120, 299, 305, 335, and 395
- These presumably have been formed by polymerization of glucose itself, or of its degradation products.

3,4-DGE ?

Conclusion

- The involvement of GDPs (other than acetaldehyde), as well as several high MW entities, in chemical peritonitis.
- Using MS and LC-MS is required for detailed probing of DGPs involved in current epidemics of peritonitis.
- Episodes can be a serious threat to the credibility and acceptance (both by patients and doctors) of PD.
- Utmost care should be taken by manufacturers to prevent such accidents.

Nephrol Dial Transplant (2000) 15: 2037–2040

Nephrology Dialysis Transplantation

Original Article

Chemical peritonitis associated with high dialysate acetaldehyde concentrations

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- 21 aseptic peritonitis cases of unknown aetiology.
- All cases appeared within one month in the center with a peritonitis rate of 1 episode/26 patient months and 55 active patients on CAPD.

Clinical and demographic data on 21 chemical peritonitis cases

Patient	Age/ gender	PD since	Perit. date	Cell count	Culture/ G stain	Complaints	Treatment	Treatment dates
1	48/M	30.12.1994	23.10.1996	200	Neg/Neg	CD	–	–
2	35/F	08.07.1996	21.10.1996	600	Neg/Neg	CD	A-S/N*	21–23.10.1996
3	64/M	16.08.1995	23.10.1996	1300	Neg/Neg	CD	–	–
4	46/M	27.10.1995	21.10.1996	800	Neg/Neg	CD, AP	A-S/N*	21–23.10.1996
5	66/M	12.06.1996	18.10.1996	3300	Neg/Neg	CD	A-S/N*	18–23.10.1996
6	53/M	06.06.1995	22.10.1996	3500	Neg/Neg	CD	A-S/N*	22–23.10.1996
7	46/M	11.01.1996	22.10.1996	1400	Neg/Neg	CD, AP	A-S/N*	22–23.10.1996
8	53/M	23.10.1992	21.10.1996	400	Neg/Neg	CD, AP	A-S/N*	21–23.10.1996
9	26/F	12.01.1995	22.10.1996	200	Neg/Neg	CD, AP	–	–
10	47/M	08.04.1996	23.10.1996	9700	Neg/Neg	CD, AP	A-S/N*	23–24.10.1996
11	37/F	27.10.1993	30.10.1996	400	Neg/Neg	CD	–	–
12	63/F	22.12.1994	18.10.1996	1300	Neg/Neg	CD	A-S/N*	18–23.10.1996
13	40/F	28.12.1993	24.10.1996	300	Neg/Neg	CD, AP, Vom	–	–
14	39/F	26.06.1996	25.10.1996	300	–	CD	A-S/N*	25–30.10.1996
15	46/M	12.04.1992	16.10.1996	200	Neg/Neg	CD	–	–
16	48/F	11.07.1995	23.10.1996	300	Neg/Neg	CD, AP	–	–
17	69/F	18.03.1996	15.10.1996	7500	Neg/Neg	CD, AP	A-S/N*	15–23.10.1996
18	57/M	10.06.1996	02.10.1996	1600	Neg/Neg	CD, AP	Ofl/Vanc**	02–23.10.1996
19	39/M	22.07.1996	21.10.1996	1900	Neg/Neg	CD, AP	A-S/N*	21–30.10.1996
20	37/F	25.09.1996	11.11.1996	2200	Neg/Neg	CD, AP	A-S/N*	11–18.11.1996
21	69/M	25.04.1996	16.10.1996	300	Neg/Neg	CD	A-S/N*	16–23.10.1996

*A-S/N, 1000 mg ampicillin + 500 mg sulbactam in each (×4) 2-l bag and netilmicin 40 mg/day as single night-time intraperitoneal dose following 100 mg initial dose; **Ofl/Vanc, ofloxacin 200 mg/day p.o., following 400 mg/day p.o. initial dose, and vancomycin 2000 mg/7 days intraperitoneal dose in one 2-l bag. F, female; M, male; CD, cloudy dialysate; AP, abdominal pain; Neg, negative; G stain, Gram stain; Vom, vomiting.

- Gas chromatography. revealed acetaldehyde levels of 17-20 p.p. m. (6 p.p.m.).
- The manufacturer reviewed its heat sterilization process in the production line and reportedly stopped the use of PH 5.9 L-lactate and replaced it with pH 5.3 L-lactate.
- Following that revision in the heat sterilization process, acetaldehyde concentrations in the bags were below 6 p.p.m., no further unusual complaints occurred during the use of locally produced PD fluids in Turkey.

CONCLUSIONS

- That higher levels of acetaldehyde and possibly other glucose degradation products may have been an aetiological factor in these 21 cases of chemical peritonitis.
- Acetaldehyde, in concentrations 3-4 times higher than the usual level in commercially available PD solutions, may induce acute sterile peritonitis in CAPD patients.

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0896-8608/10 $3.00 + .00

PD IN THE DEVELOPING WORLD

DESCRIPTION OF AN OUTBREAK OF ACUTE STERILE PERITONITIS IN IRAN

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- Between 6 March and 7 June 2006, an outbreak of sterile peritonitis occurred in 20 of the 282 CAPD patients in our CAPD center.

Clinical and Demographic Characteristics of Twenty Patients with Chemical Peritonitis

Patient	Age/ gender	Cause of CRF	PD since	Peritonitis date	Complaints	WBC count	PMN%	Culture/ Gram stain	Treatment	Treatment days	Outcome
1	50/F	Unknown	23 Jan 2005	6 Apr 2006	CD, AP	100	80	Neg/Neg	No	—	Active on PD
2	69/F	PKD	15 Jun 2005	21 Mar 2006	CD	800	97	Neg/Neg	Cefa	2	Active on PD
3	53/F	HTN	10 Mar 2005	11 Apr 2006	CD, constipation	700	80	Neg/Neg	No	—	Active on PD
4	51/F	PKD	16 Nov 2005	6 Mar 2006	CD, AP	200	40	Neg/Neg	Cefta, cefa	12	Active on PD
5	39/M	Others	20 Oct 2005	7 Jun 2006	CD	400	60	Neg/Neg	No	—	Active on PD[a]
6	62/F	HTN	9 Jul 2005	5 Apr 2006	CD, AP	500	50	Neg/Neg	Van	3	Active on PD
7	33/F	Unknown	17 Jul 2005	4 Apr 2006	AP	100	85	Neg/Neg	No	—	Active on PD
8	31/M	Unknown	24 Nov 2003	11 Mar 2006	CD, AP	600	60	Neg/Neg	Cefa, cefta	10	Active on PD
9	37/F	Unknown	19 Sep 2005	10 Apr 2006	CD, AP	400	60	Neg/Neg	No	—	Active on PD
10	55/F	DM	17 Oct 2005	13 Apr 2006	CD, AP	500	50	Neg/Neg	No	—	Active on PD
11	31/M	HTN	27 Oct 2005	3 Apr 2006	CD, AP, diarrhea	600	60	Neg/Neg	Cefa	5	Active on PD[a]
12	30/F	HTN	25 Aug 2005	17 Apr 2006	CD, AP, vomiting, fever	400	50	Neg/Neg	No	—	Active on PD
13	29/F	Others	15 Jul 2004	4 Apr 2006	CD, AP	540	60	Neg/Neg	No	—	Active on PD
14	65/M	HTN	13 Feb 2004	12 Mar 2006	CD	700	73	Neg/Neg	Cefa	10	Active on PD
15	64/F	DM	6 Jun 2003	12 Mar 2006	CD	780	55	Neg/Neg	Ceftria, cefa	10	Active on PD
16	38/F	HTN	16 Mar 2004	29 Apr 2006	CD, AP, vomiting	1600	98	Neg/Neg	No	—	Active on PD
17	61/M	DM	25 Jun 2005	19 Mar 2006	CD, AP	190	65	Neg/Neg	Cefta, van	5	Active on PD[b]
18	63/F	HTN	13 Oct 2002	21 Mar 2006	CD	800	97	Neg/Neg	No	—	Active on PD
19	72/F	HTN	27 Oct 2005	18 Mar 2006	CD, fever	400	14	Neg/Neg	Cefta, van	5	Active on PD
20	45/F	Unknown	7 Feb 2004	6 Apr 2006	CD, AP, vomiting	100	70	Neg/Neg	No	—	Active on PD

TABLE 2
Transport Data and Glomerular Filtration Rate (GFR) Before and After Acute Chemical Peritonitis (ACP)

	Before ACP	After ACP	*p* Value
D/P creat	0.55±0.1	0.77±0.07	0.036
GFR	4.9±2.53	4.5±2.95	0.62

D/P creat = dialysate-to-plasma ratio of creatinine.

measurements before and after ACP was 3.8 ± 2.5 and 3.3 ± 2.5 months respectively.

Analysis of the unused PD solution showed

- Endotoxin (0.06 endotoxin unit/mL),
- 5-hydroxymethyl furaldehyde (8 mmg/mL),
- Acetaldehyde (0.4 mmg/mL) concentrations

Conclusion

- Although chemical peritonitis in glucosebased PD solution is uncommon, it should be distinguished from bacterial peritonitis in outbreaks of peritonitis.
- Facilities to measure glucose degradation products are required, especially in developing countries.

How did we deal with the problem?

After we informed the manufacturer about the problem,

- The manufacturer reviewed the heat sterilization process in the production line and found that the *heat detector of the autoclave was impaired.* This detector was repaired in cooperation with Baxter Corporation. Since then, no unusual patient complications have occurred with the use of locally produced PD fluids in Iran!!!!!
- Measurement of GDPs??
- The kind of GDPs?
- How was the problem solved?

An acute chemical peritonitis with more than 400 cases have recently occurred

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Original Article

Cytotoxic Glucose Degradation Products in Fluids for Peritoneal Dialysis

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- This observation was carried out after the complaint of 224 renal failure patients (104 females and 120 males) who have been under continuous (PD) treatment.

Table 1. Amount of acetaldehyde in three different Lots of peritoneal dialysis solutions,* n = 3.

	Before sterilization*	After sterilization*
Lot 1	1.76±1.1	19.9±1.5
Lot 2	1.69±1.5	19.7±1.3
Lot 3	1.78±1.8	20.5±1.7

- It is proved that the commercially available single-chamber bag peritoneal dialysis fluids have cytotoxic effects in *in-vitro* studies because of the electrolytes and glucose as osmotic agents, which convert to glucose degradation products during heat sterilization and storage
- Therefore, it is suggested that the responsible company should use double-chamber modern technology, or improve the heat-sterilization process.

Conclusion

- High prevalence of chemical peritonitis in Iran in spite of rare this condition in the world
- New technology such as high pressure liquid chromatography and liquid chromatography mass spectrometry analysis for measurement of GDPs especially 3,4-DGE
- Use of biocompatible PD solution