

Bulletin de la Dialyse à Domicile

Diagnostic and therapeutic management of hydrothorax in peritoneal dialysis The Strasbourg experience in 11 cases

(Prise en charge diagnostique et thérapeutique de l'hydrothorax en dialyse péritonéale
L'expérience Strasbourgeoise à propos de 11 cas)

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Résumé

L'hydrothorax est une complication mécanique rare de la dialyse péritonéale (DP) qui aboutit souvent à une sortie de la technique. Son incidence est estimée selon les études de 1,6 à 2 %. Sa localisation est dans la majorité des cas à droite. Il est secondaire au passage du dialysat de la cavité péritonéale vers l'espace pleural à travers une brèche diaphragmatique, qui peut être acquise ou congénitale.

Les examens complémentaires nécessaires pour affirmer le diagnostic sont souvent invasifs et coûteux et ne font l'objet d'aucun consensus. Il en est de même pour la prise en charge thérapeutique qui va de la simple interruption transitoire de la dialyse à des traitements lourds comme la thoracotomie.

Dans notre centre, nous avons opté pour une simplification de la prise en charge des patients présentant un hydrothorax. Sur le plan diagnostique, nous avons recours à des examens simples, peu invasifs et moins coûteux.

Pour la prise en charge thérapeutique nous avons opté, depuis notre premier cas en 2000, pour une technique chirurgicale, simple et moins agressive avec un abord abdominal et non thoracique permettant la mise en place d'une prothèse sous diaphragmatique par voie coelioscopique pour colmater les brèches.

Sur 10 patients opérés, 2 (20%) ont présenté une récurrence de l'hydrothorax et ont été transférés définitivement en hémodialyse. Les 8 autres (80%) ont pu reprendre la DP sans récurrence ou complication ultérieure, après une période d'arrêt de la DP de 3 à 4 semaines pendant laquelle les patients étaient tous hémodialisés sur un cathéter central simple.

Mots clés: hydrothorax, communication pleuropéritonéale, pleurodèse, dialyse péritonéale

Summary

Hydrothorax is a rare mechanical complication of peritoneal dialysis (PD) which often results in discontinuation of the technique. According to studies, its incidence is estimated at 1.6 to 2%. In the majority of cases, its location is on the right. It is secondary to the passage of dialysate from the peritoneal cavity to the pleural space through a diaphragmatic breach, which may be acquired or congenital. The additional tests necessary to confirm the diagnosis are often invasive and expensive, and are not the subject of any consensus. It is the same for the therapeutic management, which goes from the simple transient interruption of the dialysis to heavy treatments such as thoracotomy. In our center, we have opted to simplify the management of patients with hydrothorax. From a diagnostic standpoint, we use simple, minimally invasive and less expensive examinations. For the therapeutic management, we have opted, since our first case in 2000, for a simple and less aggressive surgical technique, with an abdominal and non-thoracic approach allowing the installation of a sub-diaphragmatic prosthesis by laparoscopic route to seal the lesions breaches. Out of 10 operated patients, 2 (20%) presented with a relapse of hydrothorax and were permanently transferred to hemodialysis. The remaining 8 (80%) were able to resume PD without subsequent recurrence or complications, after a 3- to 4-week PD interruption period during which all patients were hemodialyzed through a simple central catheter.

Key words : Hydrothorax, Peritoneal dialysis, Pleurodesis, Pleuroperitoneal communication,

INTRODUCTION

Although hydrothorax is rare, it is a recognized mechanical complication of peritoneal dialysis (PD); according to studies, its incidence is estimated from 1.6% to 2% [1,3]. In the majority of cases—88%, according to Nomoto—it is located on the right [1]. It was first described in 1967 by Edwards and Unger [2]. Since then, several cases have been reported in the literature.

PD hydrothorax is a serious complication, leading in approximately 50% of cases to abandonment of the technique (1) due to a lack of rapid diagnosis and effective management. Proposing an alternative to systematic and definitive transfer to hemodialysis would make it possible to maintain a good number of patients on PD.

In the absence of standard diagnostic tests, several tests have been used to confirm pleuroperitoneal communication. Biochemical analysis of pleural fluid shows fluid of a transudative nature, with a glucose concentration higher than blood glucose when using glucose solution [4]. In addition, in patients treated with icodextrin, the liquid turns blue-black in the presence of iodine [5]

Peritoneal scintigraphy is one of the most widely used tests. Computed tomography and MRI are also commonly used diagnostic techniques [6,7,8]. Methylene blue testing in the peritoneal cavity has been suggested for diagnosis, but can have serious side effects such as chemical peritonitis [9], and is therefore not recommended. The use of indocyanine green as a diagnostic test was found to be of interest in a one-case study [10].

On the therapeutic level, several options have been proposed. Sufficient transient arrest of PD has been used in 53% [1] and chemical pleurodesis (talc, tetracycline, autologous blood) in 48% of cases. The application of a fibrin adhesive (Tissucol) made it possible to obtain a permanent correction of the hydrothorax in a study of a single case [11]. Other methods include video-assisted thoracoscopy, one of the most widely used options, whose success rate is 72 to 88% [12, 13] and finally thoracotomy, which, although it is an effective technique with 100% success according to a study [1], remains a very invasive procedure.

In our center, we have opted for simpler and inexpensive examinations for the management of this complication. For example, in our CHU, the cost of a simple chest x-ray amounts to 24.66 euros, a chest CT scan to 123.07 euros and a peritoneal scintigraphy to 268.87 euros.

On the therapeutic level, we use a new, less aggressive surgical technique, developed in 2000 by the digestive surgery team of Prof. MUTTER at the Strasbourg University Hospital. This technique has the distinction of using the abdominal approach and not the thoracic approach to correct the diaphragmatic abnormality [14]. The results are very encouraging, since out of 10 operated patients, only 2 (20%) presented a relapse of hydrothorax and were transferred definitively to hemodialysis. The other 8 cases (80%) were all operated on successfully and were able to resume PD without recurrence or subsequent complications, after a period of discontinuation of PD ranging from 3 to 4 weeks. During this period, the patients were all on hemodialysis on single central catheters.

PHYSIOPATHOGENIC MECHANISMS

Different mechanisms have been proposed to explain the trans-diaphragmatic passage of intraperitoneal fluid into the pleural space. One of the first to be implicated is a pre-existing diaphragmatic anomaly [15], exacerbated by the increase in intra-abdominal pressure linked to the presence of the fluid in the peritoneal cavity. This rise in pressure is believed to be the cause of the formation of blebs, or peritoneo-pleural bubbles, in areas of weakness in the tendon portion of the diaphragm. These bubbles can rupture and create gaps, allowing peritoneal fluid to pass into the pleural cavity, as in the case of hepatic hydrothorax. Emerson, in 1995, first described diaphragmatic fenestration in a patient with cirrhosis and pleural effusion [16]. Other recent studies have demonstrated the existence of such diaphragmatic defects in a large number of patients with hepatic hydrothorax [16, 17]. An increased incidence of hydrothorax has also been observed in patients with polycystic kidney disease, who often experience increased abdominal pressure associated with organomegaly [18].

Other mechanisms, such as lymphatic drainage disorder, congenital diaphragmatic breaches, traumatic diaphragmatic breaches, or a history of previous surgeries, have been implicated.

Hydrothorax in PD is not a complication specific to adults; it also affects the pediatric population, and several cases have been described in the literature. For Krichnan, the gradual increase in the volume of intraperitoneal dialysate from 10 to 40 ml / kg over 6 days would prevent the occurrence of hydrothorax in children [19].

Butani and Polinsky noted a curious association between acute hydrothorax and hemolytic uremic syndrome (HUS) in children treated with peritoneal dialysis. In fact, out of 176 children treated with peritoneal dialysis from 1982 to 1996, 34 had HUS and 142 had acute renal failure from other etiologies. Seven of the 34 children (20%) developed hydrothorax [20].

PATIENTS AND METHODS

Between the opening of our peritoneal dialysis unit in 1991 and December 31, 2020, 680 patients were treated, of whom 492 were on continuous ambulatory peritoneal dialysis (CAPD) and 188 on automated peritoneal dialysis (APD). Their mean age was 61.9 ± 18 and the sex ratio was 1.34, with 389 men and 291 women.

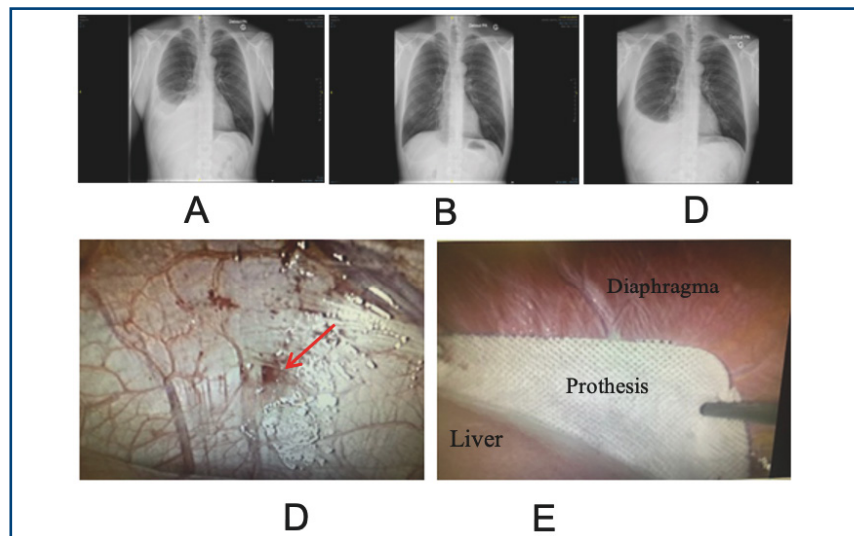
Eleven patients out of the total of 680 developed hydrothorax (individual patient details are shown in Table I). The incidence rate was 1.61% (11/680), comparable to rates reported elsewhere in the literature [1]. Seven patients were female (63.6%) and 4 were male (36.4%), aged 22 to 72 years (mean 47 years). Of the 11 hydrothoraxes, 10 were on automated peritoneal dialysis (APD) and 1 on CAPD, as this was rapidly installed 24 h after the start of PD. All the effusions were from the right side. The interval between the start of peritoneal dialysis and hydrothorax varied from 1 day to 3 years. We found no obvious explanation for the predominance of DPA over DPCA in the population of patients who presented with hydrothorax.

↓ Table 1. Characteristics of patients who developed a hydrothorax

Patient	Age	Néphropathy	PD start	Date of Hydrothorax	Delay (days)	Date of surgery	Delay (days) Dc-operation	Evolution
1	22	IgA	20/03/00	03/0400	14	13/04/00	10	PD resumed without recidive
2	72	Vascular	14/09/06	08/04/07	206	29/05/07	51	PD resumed without recidive
3	63	IgA	14/05/07	15/05/07	1	18/05/07	3	PD resumed with recidive
4	46	IgA	26/08/08	15/09/08	20	25/11/08	70	PD resumed without recidive
5	37	Return from graft	28/12/09	15/02/10	49	03/03/10	17	PD resumed with recidive
6	55	Proliferative membrane	24/09/12	18/12/12	85	07/02/13	49	PD resumed without recidive
7	47	Return from graft	26/03/13	28/03/13	186	Refus	0	Definitively transferred to HD
8	43	Return from graft	09/04/13	06/05/13	27	23/05/13	17	PD resumed without recidive
9	49	Nephrotoxicity	22/11/12	13/01/16	1147	26/01/16	13	PD resumed without recidive
10	34	Diabetic nephropathy	29/05/17	23/11/17	178	18/12/17	25	PD resumed without recidive
11	45	Return from graft	13/02/19	26/03/17	41	29/03/17	3	PD resumed without recidive

Our first case of hydrothorax was diagnosed in 2000, in a 20-year-old patient treated with APD for chronic kidney disease secondary to IgA nephropathy.

The diagnosis of hydrothorax secondary to peritoneal leakage was made on the basis of a combination of clinical, biochemical and radiological findings. Our first line of practice was to stop PD until hydrothorax completely resolved. The resumption of PD resulted in the reappearance of the effusion on the same side 24 hours later. This result was sufficient for us to confirm the existence of a diaphragmatic breach and to entrust the patient to the surgeon to seal it (Figure 1).



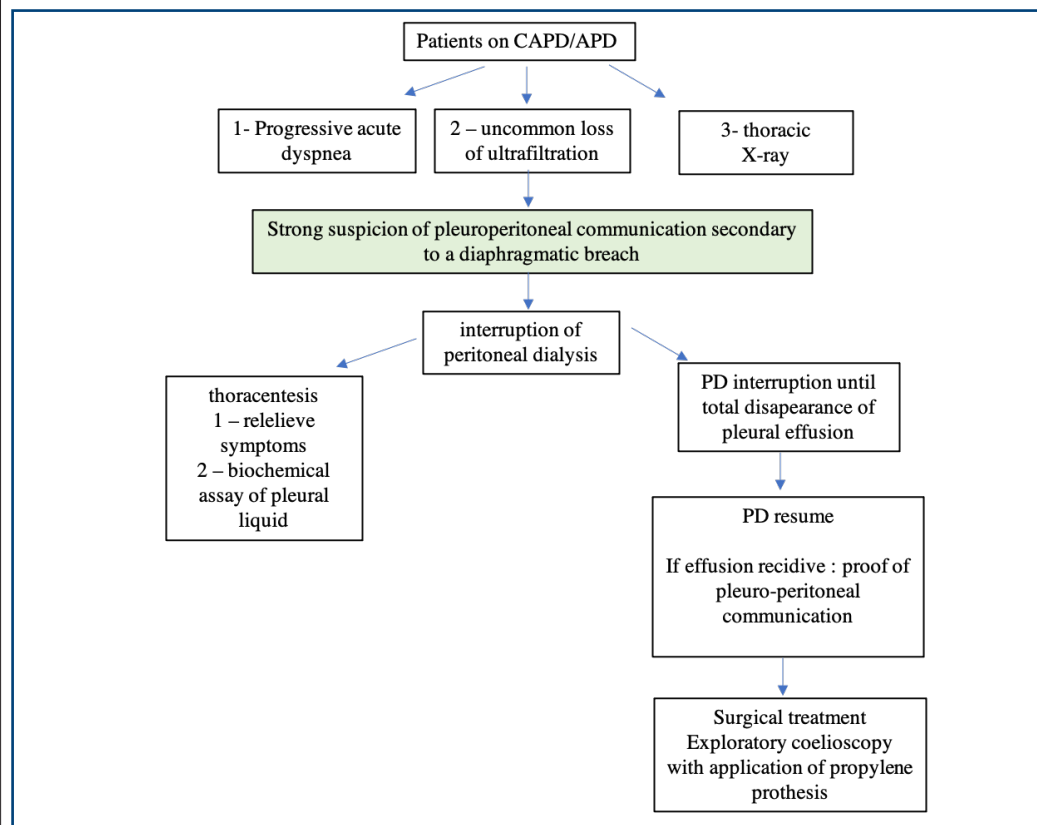
↑ Figure 1. A: D1 Right hydrothorax: stoppage of PD - B: D 9 total resolution of hydrothorax - C: D10 recurrence of hydrothorax 24 hours after resumption of PD D: diagnosis of the breach under laparoscopy - E: placement of the prosthesis under laparoscopy

The surgeon opted for an abdominal approach to treat the diaphragmatic breach, with the performance of an exploratory, diagnostic and therapeutic laparoscopy. This, on one hand, revealed a weakness in the tendinal portion of the right diaphragm, with the presence of a fibrous breach and, on the other hand, allowed the placement of a subdiaphragmatic polypropylene prosthesis to allow adhesion and closure of the breach (Figure 1). The postoperative consequences were simple. The patient was able to return home 48 hours after the operation and was temporarily transferred to hemodialysis.

After 3 weeks of peritoneal rest, the PD was resumed without any particular incident. The patient was able to resume treatment for several months without a recurrence of hydrothorax until his kidney transplant.

The case of hydrothorax in CAPD (1/11) occurred 24 hours after onset of PD. This was a 63-year-old patient treated for chronic renal failure secondary to IgA nephropathy. Pleural effusion was confirmed by chest x-ray, and the diagnosis of congenital diaphragmatic breach was made due to rapid onset of pleural effusion associated with significant loss of ultrafiltration. The patient was operated on, but the resumption of PD two weeks after the operation was complicated by a recurrence of the pleural effusion. In retrospect, we believe that the 2-week period between the operation and the resumption of dialysis was too short. The patient was transferred definitively to hemodialysis.

Since our first case of hydrothorax, we have implemented an algorithm that allows us to diagnose pleuroperitoneal communication in any pleural effusion in a patient on peritoneal dialysis (Figure 2).



↑ Figure 2. Algorithm for diagnostic and therapeutic management of a hydrothorax in patients on peritoneal dialysis

When a patient in PD, whether in APD or CAPD and regardless of his seniority in the technique, suddenly presents with progressive acute dyspnea with an unusual loss of ultrafiltration, the first examination we perform is a chest x-ray. If a right unilateral pleural effusion is visualized, the first diagnosis mentioned is that of pleuroperitoneal communication on diaphragmatic breach and PD is stopped transiently until the effusion has completely disappeared. The reappearance of the effusion on the same side after resumption of PD can only be a major witness to the presence of a diaphragmatic breach at the origin of the passage of dialysate from the peritoneal cavity to the pleural space. In this case, the patient is referred to the surgeon for an exploratory diagnostic and therapeutic laparoscopy (Figure 1).

SURGICAL PROCEDURE

Laparoscopic management of hydrothorax in peritoneal dialysis

The patient is under general anesthesia in the supine position with the legs apart and the arms at their sides. A 12 mm trocar for the camera is placed over the umbilicus, and two 5 mm trocars on the right subcostal margin. After confirmation of the diaphragmatic breach, a nonabsorbable polypropylene prosthesis with a size of 13 x 8 cm, which may vary depending on the patient's anatomy and the extent of the breaches, is placed in the sub- region. The prosthesis is fixed with two points on the membranous part of the diaphragm. The adhesion of the prosthesis to the diaphragm is then ensured by the right lobe of the liver, which holds it in place, and checked during exsufflation of the pneumoperitoneum. PD is stopped for at least 3 weeks to promote the development of a fibrous area (Figure 1):

DISCUSSION

Peritoneal dialysis and hemodialysis are two recognized treatment options in the management of advanced chronic kidney disease. They are complementary and not competitive, equivalent in terms of long-term results and life expectancy [21]. However, peritoneal dialysis has a number of advantages for the patient's quality of life and involves substantial savings [19].

PD also has some specific drawbacks and complications, among which are infectious complications such as peritonitis, infections of the emergence of the PD catheter and those related to increased intra-abdominal pressure under the effect of dialysate in the peritoneal cavity, such as abdominal hernias, in particular umbilical hernia [22] and leakage of dialysate out of the peritoneal cavity, for example pleural effusion [2]. The increase in intra-abdominal pressure generated by intra-peritoneal fluid is considered to be one of the most important risk factors for peritoneal leakage into the pleural space and, due to increased intra-abdominal pressure, this complication is more frequently described in patients with polycystic kidney disease [18].

The adequate management of hydrothorax in PD largely depends on the early diagnosis and the effectiveness of the surgical treatment, and any ignorance of this complication most often leads to the abandonment and failure of the technique.

Thus, the diagnosis of hydrothorax should be systematically discussed in the presence of any progressive acute dyspnea associated with pleural effusion and unusual loss of ultrafiltration. Interrupting PD should be one of the first steps to take to prevent the progression of the effusion

and the worsening of the clinical picture.

In the literature, several diagnostic tests have been used to confirm the peritoneal origin of hydrothorax in PD, but no test has shown high sensitivity. Peritoneal scintigraphy is one of the most widely used techniques, but its sensitivity is only 40% to 50% [7,8]. Contrast computed tomography peritoneography is associated with a sensitivity of 33% according to one study [7,8] and the methylene blue test is associated with a risk of chemical peritonitis [9].

In our center, the occurrence of any right acute pleural effusion in a PD patient is considered, until proven otherwise, as pleuro-peritoneal communication. The diagnosis is based on clinical and radiological progress after transient stopping of PD, then resumption.

Our results are very encouraging, since out of 10 operated patients only 2 (20%) presented a relapse of hydrothorax and were transferred definitively to hemodialysis. The other 8 cases (80%) were all operated on successfully and were able to resume PD without recurrence or subsequent complications, after a period of discontinuation of PD ranging from 3 to 4 weeks. During this period, the patients were all hemodialyzed on single central catheters.

In our series, it is interesting to note the absence of polycystic patients among those who presented with hydrothorax, while polycystic kidney disease was implicated in the genesis of higher intraperitoneal pressures.

In addition, of the 39 patients refolded in PD after renal transplant failure, we find that 4 presented this mechanical complication; 3 patients had their grafts on the right, and one patient had a graft on the right and another on the left. All of the patients were on immunosuppressive therapy; however, we have no medical or surgical explanation for this observation. The causes of dialysis in patients with hydrothorax are summarized in Table 1.

The times between the diagnosis of hydrothorax and the surgical intervention are variable, because the surgical correction of the diaphragmatic breach offered to our patients depends on the consent of each patient, their clinical condition and the availability of the surgeon. In most cases, they are between 3 and 25 days. In one case, patient N° 7 (Table 1) refused surgical treatment, and in a second case, patient N° 2 was hospitalized in intensive care for cardiogenic shock for several weeks. The third and fourth case patients, N° 4 and 6, preferred to try the first treatment option, which was the transient stopping of PD for several weeks.

Finally, in our hydrothorax series, we concluded that there is a physiopathological mechanism of mechanical origin (diaphragmatic breach). The diagnostic and therapeutic approach is different for hydrothorax via lymphatic communication, as shown in Kanaan's study [23].

CONCLUSION

Hydrothorax is a known but rare complication of PD, and is a cause of definitive transfer to hemodialysis in the absence of effective management. The existence of different treatment options should be presented to all patients with hydrothorax in order to avoid this transfer. The diagnosis must be systematically evoked in the event of any acute unilateral pleural effusion in a patient on peritoneal dialysis. It can be confirmed with a set of clinical and radiological criteria. Immediate

and transient discontinuation of PD should be preferred as a first-line treatment. Our satisfactory results (80% success) suggest that the minimally invasive technique consisting of the placement of a prosthesis under diaphragm by laparoscopic route could represent a powerful alternative to historical surgical techniques.

Disclosure

The authors declare no conflict of interest for this article.

Contribution of authors

Larbi Bencheikh conceived the project and wrote the article, Antonio D'Urso wrote the surgical procedure, Françoise Heibell reviewed and corrected the article.

REFERENCES

1. Nomoto Y, Suga T, Nakajima K, Sakai H, Osawa G, Ota K. Acute hydrothorax in continuous ambulatory peritoneal dialysis – a collaborative study of 161 centers. *Am J Nephrol.* 1989;9:363–367. [PubMed] [Google Scholar]
2. Edward SR, Unger AM. Acute hydrothorax: a new complication of peritoneal dialysis. *JAMA.* 1967;199:853–855. [PubMed] [Google Scholar]
3. Szeto, C.C. , Chow, K.M. Pathogenesis and management of hydrothorax complicating Peritonealdialysis. *Curr Opin Pulm Med* 2004;10: 315–19. [Google Scholar] |Crossref | [Medline]
4. Momenin N, Colletti PM, Kaptein EM. Low pleural fluid-to-serum glucose gradient indicates pleuroperitoneal communication in peritoneal dialysis patients: presentation of two cases and review of the literature. *Nephrol Dial Transplant* 2012; 27: 1212–1219 [PubMed] [Google Scholar]
5. Camilleri B, Glancey G, Pledger D, et al. The icodextrin black line sign to confirm a pleural leak in a patient on peritoneal dialysis. *Perit Dial Int* 2004; 24: 197. [PubMed] [Google Schola]
6. Huang, J.J. , Wu, J.S. , Chi, W.C. , Lan, R.R. , Yang, L.F. , Chiu, N.T. Hydrothorax in continuous ambulatory peritoneal dialysis: therapeutic implications of Tc-99m MAA peritonealscintigraphy. *Nephrol Dial Transplant* 1999;14: 992–7. [Google Scholar | Crossref | Medline]
7. Pankaj P, Pathak V, Sen IB, Verma R, Bhalla AK, Marwaha A, Pandey S. Use of radionuclide peritoneography in the diagnosis of pleuroperitoneal communication as a complication of continuous ambulatory peritoneal dialysis. *Ind J Nucl Med.* 2005;20:4–8. [Google Scholar]
8. Tang S, Chui WH, Tang AW, Li FK, Chau WS, Ho YW, Chan TM, Lai KN. Video-assisted thoracoscopic talc pleurodesis in effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. *Nephrol Dial Transplant.* 2003;18:804–808. [PubMed] [Google Scholar]
9. M. Macia, E. Gallego, I. Garcia-Cobaleda, J. Chahin, and J. Garcia, “Methylene blue as a cause of chemical peritonitis in a patient on peritoneal dialysis,” *Clinical Nephrology*, vol. 43, no. 2, pp. 136-137, 1995
10. Jun Young Lee, Jae-Won Yang, Seung Ok Choi, Byoung- Geun Han. Utility of indocyanine green for diagnosing peritoneal dialysis related hydrothorax. *Kidney Research and Clinical Practice* 2018;37(4):423
11. Jannis Vlachoianis, Ivar Boettcher, Lothar Brandt, Wilhelm Schoeppe. A new Treatment for Unilateral Recurrent Hydrothorax during CAPD, *Peritoneal Dialysis International*, vol. 5, 3: pp. 180-181. 1985
12. Chow KM, Szeto CC, Li PKT. Options de gestion de l'hydrothorax compliquant l'analyse péritonéale. *Séminaire Dial.* 2003; 16: 389–94.
13. Saito M, Nakagawa T, Tokunaga Y, Kondo T. Traitement chirurgical thoracoscopique pour la communication pleuropéritonéale. *Intéragir Cardiovasc Thorac Surg.* 2012; 15: 788–9

14. Didier Mutter, Cosimo Callari, Michele Diana, Larbi Bencheikh, Françoise Heibel, Jacques Marescaux. A Novel Technique to Treat hydrothorax in Peritoneal Dialysis: Laparoscopic Hepato-diaphragmatic Adhesion. *Perit Dial Int* Nov-Dec 2011;31(6):692-4
15. G. Del Peso, M.A. Bajo, O. Costero, C. Hevia, F. Gil, C. Díaz, et al. Risk factors for abdominal wall complications in peritoneal dialysis patients. *Perit Dial Int*, 23 (2003), pp. 249-254
16. Emerson, FA, Davies, TH Hydrothorax compliquant l'ascite. *Lancet* 1995 ; 1: 487 . [Google Scholar]
17. Lieberman, F. , Hidemura, R. , Peters, R. , Reynolds, T. Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. *Ann Int Med* 1966; 64: 341–51. [Google Scholar | Crossref | Medline]
18. Fletcher, S. , Turney, J.H. , Brownjohn, A.M. Increased incidence of hydrothorax complicating peritoneal dialysis in patients with adult polycystic kidney disease. *Nephrol Dial Transplant* 1994; 9: 832–3. [Google Scholar | Medline]
19. Krishnan, R.G. , Ognjanovic, M.V. , Crosier, J. , Coulthard, M.G. Acute hydrothorax complicating peritoneal dialysis. *Perit Dial Int* 2007;27: 296–9.[Google Scholar | SAGE Journal]
20. Butani, L. , Polinsky, M.S. , Kaiser, B.A. , Baluarte, H.J. Pleural effusion complicating acute peritoneal dialysis in hemolytic uremic syndrome. *Pediatr Nephrol* 1998; 12: 772–4. [Google Scholar | Crossref | Medline]
21. Mehrotra, R. , Chiu, Y.W. , Kalantar-Zadeh, K. , Bargman, J. , Vonesh, E. Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch Intern Med* 2011; 171: 110–18. [Google Scholar | Crossref | Medline]
22. R. Garcia Ramon and A. Miguel Carrasco, "Hydrothorax in peritoneal dialysis," *Peritoneal Dialysis International*, vol. 18, no. 1, pp. 5–10, 1998. View at: [Google Scholar]
23. Nada Kanaan, Thierry Pieters, Francois Jamar, Eric Goffin Hydrothorax complicating continuous ambulatory peritoneal dialysis: successful management with talc pleurodesis under thoroscopy. *Nephrol Dial Transplant* (1999) 14: 1590-1592

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