THE OCCURRENCE OF INCREASED INTRAPERITONEAL VOLUME EVENTS IN AUTOMATED PERITONEAL DIALYSIS IN THE US: ROLE OF PROGRAMMING, PATIENT/USER ACTIONS AND ULTRAFILTRATION

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◆ **Background, objectives and methods:** Increased intra-peritoneal volume (IIPV) can occur during automated peritoneal dialysis (APD). The contribution of factors such as cyclor programming and patient/user actions to IIPV has not been previously explored. The relationship between IIPV and cyclor programming, patient/user actions, and ultra-filtration over a two-year period was investigated using US data from Baxter cyclors. Drain/fill volume ratios of > 1.6 to ≤ 2.0 and > 2.0 were defined as Level I and Level II IIPV events, respectively.

◆ **Results:** Level I IIPV events occurred in 2.39% of standard and 4.73% of small fill volume therapies, while Level II IIPV events occurred in 0.26% and 1.33% of therapies, respectively. IIPV events occurred significantly more often in association with tidal peritoneal dialysis (PD) compared to non-tidal PD therapies. In tidal therapies, IIPV events were primarily related to suboptimal programming of total ultrafiltration volume. Factors that increased the odds of IIPV events during standard therapies included programming the initial drain volume target to $< 70\%$ of the last fill, and setting minimum drain volumes to $< 85\%$ of the fill volume. Bypass of initial drain by patients/users was also associated with a significant increase in the odds of IIPV events in non-tidal, but not tidal PD. An increase in the odds for IIPV was also seen for standard therapies within the highest ($> 1,245$ mL) versus the lowest (< 427 mL) quartile of ultrafiltration. Similar trends were seen in small fill volume therapies. Clinical presentations associated with IIPV events were not assessed.

◆ **Conclusions:** IIPV events are more frequent in tidal and small fill volume therapies. The greatest potential for IIPV occurred when the total ultrafiltration was set too low for the patient's UF requirements during tidal therapy. Patient/user bypass of drains without reaching the target drain volume contributes significantly to IIPV events in non-tidal PD

therapies. Poorly functioning PD catheters may be central to the cyclor programming and patient/user actions that lead to IIPV.

Perit Dial Int 2014; 34(4):434–442 www.PDConnect.com
doi:10.3747/pdi.2013.01157

KEY WORDS: Automated peritoneal dialysis; increased intraperitoneal volume; ultrafiltration; tidal peritoneal dialysis.

Automated peritoneal dialysis (APD) is currently the predominant means of peritoneal dialysis (PD) delivery in the United States (US) with more than 70% of the US PD patient population using this therapy in 2006 (1). Notably, the utilization of APD is increasing worldwide (2). Outcomes for PD patients are improving more than for hemodialysis (HD) patients, however, outcomes of dialysis patients overall are not optimal, reinforcing the need to investigate and address any potentially modifiable contributing factors (3–5).

Increased intraperitoneal pressure (IPP) from increased intraperitoneal volume (IIPV) has been associated with abdominal or back pain, dialysate leakage into the abdominal wall, genital tissues, or pleural cavity, and shortness of breath in adults and children (6). More serious infrequent complications in adults and children include severe respiratory distress, hydrothorax (7–8), and pericardial effusions (9). PD patients with pre-existing cardiac disease or compromised pulmonary function may be more susceptible to the physiologic effects of IIPV or IPP since increases in either parameter are associated with decreased cardiac output (10–11), elevated blood pressure (12), decreased pulmonary compliance, hypoxia and hypercapnia (13), and decreased pulmonary volumes (14).

Unintended IIPV (further called IIPV), often referred to as “overfill”, occurs when there is more than the desired amount of fluid in the abdomen at any time during the

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Received 20 June 2013; accepted 7 September 2013.

therapy. This may result from prescription/programming errors, insufficient drain of dialysate effluent, or APD device (cycler) malfunction. Recently, the US Manufacturer and User Facility Device Experience (MAUDE) database was reviewed to determine the relationship between the drain volume (DV) and prescribed fill volume (FV), expressed as the DV/FV ratio (15). The analysis revealed an association between increased DV/FV and adverse clinical events, although significant patient-to-patient variability was noted with respect to intraperitoneal volume (IPV) tolerance. A preliminary investigation of cycler Device Log Files (DLFs) by the Baxter Healthcare Corporation and DEKA Research and Development teams in 2010 suggested that the primary root causes of unintended IIPV were related to inappropriate prescriber cycler programming and/or inappropriate actions by patients/users such as bypassing drain cycles.

To better understand the relationship between the frequency of IIPV events and either prescription/programming settings or patient/user actions, we performed a systematic evaluation of data from APD cyclers returned for routine maintenance or due to a complaint. We hypothesized that an increased occurrence of IIPV events would be associated with setting drain volume percent targets too low, setting the estimated total ultrafiltration (UF) with tidal PD (TPD) inappropriately low, bypassing drain cycles prematurely, and having a relatively high cycler UF during the night APD therapy.

METHODS

STUDY POPULATION

DLFs were assessed from HomeChoice or HomeChoice Pro (Baxter Healthcare Corporation, Deerfield, IL, USA) cyclers with software version 10.210 returned for routine maintenance or a complaint investigation between October 1, 2009, and September 30, 2011. Only complete therapies with full log history (including programmed patient prescription, UF volumes, alarms, and patient-initiated events such as bypass activities) and at least three completed therapy cycles were analyzed. Approximately 33,000 DLFs representing approximately 116,500 therapies meeting these criteria were imported into a database and queried using Microsoft SQL Server 2005. All cycler data were devoid of identifiable patient information.

STUDY VARIABLES

For the purpose of this study, standard ($> 1,000$ mL) and small ($\leq 1,000$ mL) fill volumes were analyzed

separately. Fill volumes less than or equal to 1000 mL were assumed to represent primarily pediatric patients. APD tidal therapy with and without a mid-day exchange was classified as tidal PD (TPD); similarly, APD non-tidal therapy with and without a mid-day exchange was classified as non-tidal PD (non-TPD) for this analysis.

Prescriber programming of cycler therapy settings included I-drain setting, minimum drain volume (MDV) % settings, last manual drain (LMD), and programmed UF volumes for TPD. *Patients/user actions* included activities such as bypassing I-Drain and/or night drains with/without the low drain volume alarm (LDVA). Cycler UF was calculated as the difference between total DV and total FV during the night APD therapy, and did not represent a direct measurement of UF.

The DV used in this calculation is the maximum volume of fluid that is drained in any cycle during therapy, except I-drain. Since the DV used for this calculation is usually more than the FV, particularly given an average UF volume of 8% of the FV (1,16), the DV/FV is typically > 1.0 . For non-TPD with a complete fill and drain cycle, DV is calculated as: programmed FV + cycle UF volume. It is assumed that the programmed FV is approximately equal to the actual FV. For TPD, a correction is applied to account for partial fill and drain cycles.

A DV/FV greater than 1.6 was defined as the threshold value for an increased potential for an IIPV event. This is because clinical observations including shortness of breath, abdominal or chest pain, or a decrease in forced vital capacity or cardiac output typically occur at a DV/FV ratio of at least 1.5 and greater (17–18), and evidence demonstrating the presence of an average unaccounted residual volume (RV) of 10% (19).

STATISTICAL ANALYSES

The number of IIPV events was tabulated for each standard- and small-FV therapy and DV/FV ratio (> 1.6 to ≤ 2.0 and > 2.0). For each FV and DV/FV, logistic regression analysis was performed to estimate the IIPV occurrence rates along with the odds ratios (OR) of condition 1 relative to condition 2 (e.g. TPD vs non-TPD) using SAS (SAS Institute, Cary, NC, USA) procedure GENMOD (20) assuming a binomial model with a log-link function (IIPV event = 0 if absent or 1 if present). The odds of an IIPV occurrence is the probability of an IIPV event (IIPV occurrence rate) divided by the probability of no IIPV event ($1 - \text{IIPV occurrence rate}$), or, equivalently, the number of IIPV events (x) divided by the number of therapies without an IIPV event (number of therapies $- x$). A ratio > 1.0 indicates that the condition 1 rate is greater than the condition 2 rate. Similar statistical methods were

performed to compare quartiles of UF and IIPV occurrence rates. Finally, the second to fourth UF quartiles were compared to the first UF quartile to establish the OR for IIPV.

Two-sided 95% confidence interval (CI) limits were calculated for the OR and the associated *p* value comparing the OR to the hypothesized value of 1. All statistical analyses were performed using SAS software, version 9.0 (SAS Institute Inc., Cary, NC, USA) (20).

RESULTS

OVERALL IIPV EVENT RATES

IIPV occurrence rates and OR for various prescriber programming settings and patient/user actions are summarized for standard-FV (Table 1) and small-FV therapies (Table 2). During the study period, 114,003 standard-FV and 2,559 small-FV PD therapies were identified. The overall rate of Level I IIPV events was 2.39% for standard-FV therapies and 4.73% for small-FV therapies. Level II IIPV events ($DV/FV > 2.0$) occurred in 0.26% and 1.33% of standard-FV and small-FV therapies, respectively.

IIPV EVENT RATES ASSOCIATED WITH SPECIFIC PROGRAMMED CYCLER SETTINGS

TPD was programmed in 12.1% of standard-FV and 10.7% of small-FV therapies. IIPV event rates were significantly greater with TPD compared to non-TPD in standard-FV therapies for Level I IIPV (6.84% vs 1.78%, respectively; $p < 0.001$) and Level II IIPV (0.73% vs 0.2%, respectively; $p < 0.001$), (Table 1). Differences in IIPV rates between TPD and non-TPD were more pronounced with small-FV therapies (Table 2) for both Level I IIPV (13.5% vs 3.68%, respectively; $p < 0.001$) and Level II IIPV (5.84% vs 0.79%, respectively; $p < 0.001$). Greater IIPV occurrence rates were also noted when the anticipated total UF programmed in TPD was set to zero vs > 0 (11.48% vs 5.43% for Level I, 1.19% vs 0.6% for Level II; $p < 0.001$ for both), the I-Drain alarm percentage programmed to $< 70\%$ of the last FV, and MDV percentage programmed to $< 85\%$ of FV in standard therapies (Table 1). The overall IIPV occurrence rate for programmed cycler settings with small-FV therapies was higher compared to standard-FV therapies. However, the OR for Level I IIPV events in small-FV therapies was significantly increased only when MDV was programmed to $< 85\%$. Enabling LMD, a setting that allows patients to execute an additional drain upon completion of cycler therapy if the programmed total UF target is unmet, was associated with a 27% increase ($p = 0.014$) in the Level I IIPV occurrence rate in standard-FV therapies (Table 1).

IIPV EVENT RATES ASSOCIATED WITH A PATIENT/USER DRAIN BYPASSING

Bypass of at least one drain occurred in 22.4% of standard-FV therapies and 31.1% of small-FV therapies. In standard-FV therapies, bypass of I-drain occurred in 17.7% of non-TPD and 30.4% of TPD therapies. In small-FV therapies, I-drain bypass occurred more frequently (23.3% in non-TPD vs 42.3% in TPD). Bypass of at least one drain in standard-FV therapies was associated with higher OR for both levels of IIPV (Level I OR 1.61, 95% CI 1.48 – 1.74; Level II OR 2.97, 95% CI 2.37 – 3.73; $p < 0.001$ for both) (Table 1). In small-FV therapies, the OR was significant only for Level II IIPV (OR 1.99, 95% CI 1.01 – 3.92; $p = 0.048$) (Table 2). Specifically, with bypass of I-drain in non-TPD, standard-FV was associated with a significant potential for both levels of IIPV; for small-FV group, OR for this action was significant only for Level II IIPV (OR 4.17, 95% CI 1.64 – 10.62; $p = 0.003$) (Table 2). For these non-TPD therapies, bypassing I-drain was associated with a significant increase in IIPV event rate only in the setting of a daytime dwell or “last fill” (standard-FV: Level I OR 1.48, 95% CI 1.29 – 1.69; Level II OR 2.92, 95% CI 2.06 – 4.15; $p < 0.001$ for both; small-FV: Level II OR 6.61, 95% CI 1.98 – 22.09; $p = 0.002$) (Tables 1 and 2).

As noted above, TPD was associated with increased odds of IIPV; the majority of these patients did not bypass I-drain (69.6% for standard-FV, 57.7% for small-FV, respectively). Of those TPD patients who did bypass I-drain, with or without a LDVA, this action did not result in further significant increase in IIPV event risk. This was true for both standard-FV and small-FV therapies, and was independent of the presence or absence of a daytime dwell or “last fill” (Table 1 and 2). For small-FV therapies, no Level II IIPV events occurred when users bypassed I-drain after receiving a LDVA, either during TPD or non-TPD (Table 2).

IIPV EVENTS ASSOCIATED WITH ACHIEVED UF ON THE CYCLER

Therapies associated with bypassing of I-drain were excluded from this analysis. Median UF volume on standard-FV therapy segregated into approximately 500 mL quartiles, with the lowest quartile being 150 mL (range –3,005 to 427 mL) and the highest, 1,572 mL (range 1,245 to 4,866 mL) (data not shown). Level I IIPV occurrence rate increased progressively from the first to fourth quartile of cycler UF (0.26%, 0.59%, 1.46% and 6.6% occurrence rates). Level II IIPV events were very low except for the fourth UF quartile (0.73% occurrence rate). The greatest odds for an IIPV event were seen when

TABLE 1
Increased Intraperitoneal Volume (IIPV) Occurrence Rates (%) and Effect of Programming and Patient/User Actions on IIPV Events (Standard FV >1,000 mL)

Conditions	Level I (DV/FV of >1.6≤2.0)			Level II (DV/FV of >2.0)		
	% of events	OR (95% CI)	p value	% of events	OR (95% CI)	p value
Prescriber Programming						
TPD (12.1%) vs non-TPD (87.9%)	6.84 vs 1.78	4.06 (3.74, 4.4)	<0.001	0.73 vs 0.2	3.74 (2.94, 4.76)	<0.001
Tidal Total UF = 0 mL (23.3%) vs >0 mL (76.7%)	11.48 vs 5.43	2.26 (1.97, 2.59)	<0.001	1.19 vs 0.6	2.00 (1.34, 3)	<0.001
I-Drain Volume <70% of LFV (56.9%) vs ≥70% (43.1%)	2.66 vs 1.59	1.69 (1.53, 1.87)	<0.001	0.3 vs 0.16	1.89 (1.39, 2.55)	<0.001
MDV <85% (6%) vs ≥85% (94%), non-TPD	3.34 vs 1.68	2.03 (1.75, 2.35)	<0.001	0.37 vs 0.19	1.96 (1.26, 3.06)	0.003
Last Manual Drain Enabled (3.25%) vs Disabled (96.7%)	2.99 vs 2.37	1.27 (1.05, 1.54)	0.014	0.13 vs 0.27	0.51 (0.21, 1.22)	0.130
Patient/User Actions						
Bypassing ≥1 Drain (22.4%) vs no Drain Bypasses (77.6%)	3.35 vs 2.11	1.61 (1.48, 1.74)	<0.001	0.54 vs 0.18	2.97 (2.37, 3.73)	<0.001
Bypassing I-Drain (17.7%) vs no I-Drain Bypass (82.3%), non-TPD	2.21 vs 1.68	1.32 (1.18, 1.48)	<0.001	0.38 vs 0.16	2.44 (1.82, 3.27)	<0.001
Bypassing I-Drain w/o LDVA (44.5%) vs w/ LDVA (55.5%), non-TPD	2.77 vs 1.77	1.58 (1.3, 1.94)	<0.001	0.46 vs 0.33	1.40 (0.87, 2.26)	0.164
Bypassing I-Drain (16.9%) vs no I-Drain Bypass (83.1%), non-TPD, w/ Last Fill	2.17 vs 1.48	1.48 (1.29, 1.69)	<0.001	0.39 vs 0.13	2.92 (2.06, 4.15)	<0.001
Bypassing I-Drain (20%) vs no I-Drain Bypass-non-TPD, w/o Last Fill (80%)	2.31 vs 2.33	0.99 (0.81, 1.22)	0.936	0.37 vs 0.24	1.54 (0.89, 2.65)	0.121
Bypassing I-Drain (30.4%) vs no I-Drain Bypass (69.6%), TPD	6.63 vs 6.93	0.95 (0.82, 1.1)	0.511	0.91 vs 0.66	1.38 (0.92, 2.07)	0.116
Bypassing I-Drain w/o LDVA (80.9%) vs w/ LDVA (19.1%), TPD	6.8 vs 5.89	1.17 (0.84, 1.61)	0.353	0.98 vs 0.63	1.56 (0.61, 4.01)	0.354
Bypassing I-Drain (n=3,050) vs no I-Drain Bypass, TPD w/ Last Fill (n=7,426)	6.43 vs 6.54	0.98 (0.83, 1.16)	0.824	0.79 vs 0.66	1.19 (0.73, 1.95)	0.478
Bypassing Initial Drain (n=1,125) vs No I-Drain Bypass, TPD w/o Last Fill (n=2,126)	7.11 vs 8.33	0.84 (0.64, 1.11)	0.223	1.24 vs 0.66	1.90 (0.9, 4)	0.091

DV/FV = drain volume/fill volume ratio; OR = odds ratio; CI = confidence interval; TPD = tidal peritoneal dialysis; UF = ultrafiltration; I-drain = initial drain; LFV = last fill volume; MDV = minimal drain volume; LDVA = low-drain volume alarm; w/o = without; w/ = with; FV = fill volume.

comparing fourth to first quartiles of median cyclor UF with a comparative OR of 27.03, (95% CI 20.87 – 35.01) for Level I and 28.03 (95% CI 12.41 – 63.3) for Level II.

In small-FV therapies, median UF volume quartiles segregated into approximately 200 mL increments for quartiles one to three, but doubled to median UF volume

TABLE 2
Increased Intraperitoneal Volume (IIPV) Occurrence Rates (%) and Effect of Programming and Patient/User Actions on the IIPV Events (Small FV $\leq 1,000$ mL)

Conditions	Level I (DV/FV of $>1.6 \leq 2.0$)			Level II (DV/FV of >2.0)		
	% of events	OR (95% CI)	<i>p</i> value	% of events	OR (95% CI)	<i>p</i> value
Prescriber Programming						
TPD (10.7%) vs non-TPD (89.3%)	13.5 vs 3.68	4.09 (2.72, 6.16)	<0.001	5.84 vs 0.79	7.81 (3.93, 15.5)	<0.001
Tidal Total UF=0 mL (43.8%) vs >0 mL (56.2%)	15.0 vs 12.34	1.25 (0.63, 2.51)	0.523	8.33 vs 3.9	2.24 (0.79, 6.36)	0.129
I-Drain Volume <70% of LFV (86.5%) vs $\geq 70\%$ of LFV (13.5%)	2.97 vs 4.33	0.68 (0.34, 1.36)	0.274	1.42 vs 2.16	0.65 (0.24, 1.74)	0.391
MDV <85% (13.6%) vs $\geq 85\%$ (86.4%), non-TPD	6.11 vs 3.29	1.91 (1.33, 3.23)	0.016	0 vs 0.91	0 (0,0)	NA
Last Manual Drain Enabled (1.25%) vs Disabled (98.7%)	6.25 vs 4.71	1.35 (0.32, 5.71)	0.438	3.13 vs 1.31	2.44 (0.32, 18.39)	0.387
Patient/User Actions						
Bypassing ≥ 1 Drain (31.1%) vs no Drain Bypasses (68.9%)	5.65 vs 4.31	1.33 (0.91, 1.94)	0.142	2.01 vs 1.02	1.99 (1.01, 3.92)	0.048
Bypassing I-Drain (23.3%) vs no I-Drain Bypass (76.7%), non-TPD	3.00 vs 3.88	0.77 (0.44, 1.33)	0.346	1.88 vs 0.46	4.17 (1.64, 10.62)	0.003
Bypassing I-Drain w/o LDVA (54.2%) vs w/ LDVA (45.8%), non-TPD	4.84 vs 0.82	6.16 (1.39, 27.38)	0.017	3.46 vs 0	NA	NA
Bypassing I-Drain (23.6%) vs no I-Drain Bypass (76.4%), non-TPD w/ Last Fill	1.68 vs 2.33	0.72 (0.29, 1.75)	0.463	2.24 vs 0.35	6.61 (1.98, 22.09)	0.002
Bypassing I-Drain (22.8%) vs no I-Drain Bypass (77.2%), non-TPD w/o Last Fill	5.68 vs 6.88	0.82 (0.4, 1.66)	0.575	1.14 vs 0.67	1.70 (0.31, 9.37)	0.542
Bypassing I-Drain (42.3%) vs no I-Drain Bypass (57.7%), TPD	12.93 vs 13.92	0.92 (0.45, 1.86)	0.812	3.45 vs 7.59	0.43 (0.14, 1.38)	0.158
Bypassing I-Drain w/o LDVA (82.8%) vs w/ LDVA (17.2%), TPD	13.54 vs 10	1.41 (0.29, 6.8)	0.669	4.17 vs 0	NA	NA
Bypassing I-Drain (40.5%) vs No I-Drain Bypass (59.5%), TPD w/ Last Fill	8.86 vs 12.07	0.71 (0.27, 1.84)	0.480	3.8 vs 9.48	0.38 (0.1, 1.4)	0.144
Bypassing I-Drain (47.5%) vs No I-Drain Bypass (52.5%), TPD w/o Last Fill	23.68 vs 19.05	1.32 (0.45, 3.86)	0.613	2.63 vs 2.38	1.11 (0.07, 18.35)	0.943

DV/FV = drain volume/fill volume ratio; OR = odds ratio; CI = confidence interval; TPD = tidal peritoneal dialysis; UF = ultrafiltration; I-drain = initial drain; LFV = last fill volume; MDV = minimal drain volume; LDVA = low-drain volume alarm; w/o = without; w/ = with; NA = Not Applicable.

of 838 mL (range 579–1,903 mL) in the fourth UF quartile (data not shown). Concurrent with these latter findings, the occurrence rate of Level I IIPV events was low

among the first three UF quartiles (1.68%, 1.26%, and 2.10%). However, a marked increase in IIPV occurrence rate (13.1% Level I, 3.37% Level II occurrence rates,

respectively) was seen in the highest quartile of achieved UF. No Level II IIPV events occurred in the first and second quartiles of cycler UF.

An exponential increase in IIPV events was also noted when cycler-derived UF was examined relative to the total therapy FV without a last fill for both standard and small-FV therapies (data not shown). Among patients with a standard-FV, Level I IIPV event rates increased progressively from 0.22% in the first quartile to 9.12% in the fourth quartile. As compared to an average UF/total therapy FV of 8% (1,17), the median UF in quartile four was twice this volume at 16.4% (range 12.8% to 46.3%). OR of a Level I IIPV event was highest when comparing the fourth vs the first UF quartile (OR 45.66, 95% CI 25.72 – 81.04, $p < 0.001$). Among patients with small-FV, Level I IIPV event rates increased from 1.91% in the first quartile to 21.7% in the fourth quartile of achieved UF/total therapy FV (median cycler UF in quartile four was 18.4% (range 12.0% to 40.2%)), expressed as a percentage of total therapy FV. Similar IIPV event rates were observed in all quartiles of UF when expressed as a percentage of total therapy FV including the last fill (data not shown).

An incremental progression in Level I IIPV event rate was noted with both standard-FV and small-FV therapies in association with an increasing difference between UF achieved and the UF value programmed by the clinician. The relationship between actual cycler UF and programmed (i.e. clinician-estimated) total UF with TPD is noted in Figure 1. In small-FV therapies, Level I IIPV occurrence rates were 25.64% in quartile four. The highest OR for Level I IIPV was observed with standard-FV therapy when the programmed (i.e. clinician-estimated) total UF was set to 0 or very low, but the actual cycler UF achieved was approximately eight times higher than the estimate programmed (OR 157.9, 95% CI 50.6 – 492.6).

DISCUSSION

This is the first systematic analysis of APD cycler data which evaluated the frequency of IIPV events and potential factors associated with their occurrence. Our analysis demonstrates that IIPV events occurred in 2.65% of 114,003 standard-FV and 6.06% of 2,559 small-FV therapies. However, several programming factors and patient/user-related actions were associated with increased potential for developing IIPV. Tidal PD was used in 12.1% of standard-FV and 10.7% of small-FV therapies, and significantly increased (tripled) the rates of IIPV (7.6% in standard-FV and 19.3% for small-FV therapies). Both Level I and Level II IIPV events occurred more commonly in tidal as compared to non-tidal PD treatments.

Figure 1 — Effect of actual Cycler UF/Programmed Total UF ratio on Level I (DV/FV > 1.6 ≤ 2.0) and Level II (DV/FV > 2.0) IIPV occurrence events in Tidal PD in standard fill volume therapies (A) and small fill volume therapies (B). OR = odds ratio compared to 1st Quartile in Figure 1a and 1b for Level I IIPV events; ORs not available for level II IIPV events since there were no therapies in 1st and 2nd Quartiles exceeding DV/FV of 2.0. If confidence interval does not capture 1.00, then quartile is significantly larger than 1st quartile. IIPV = increased intraperitoneal volume; UF = ultrafiltration; DV/FV = drain volume/fill volume ratio; N/A = not applicable.

Odds ratios for both Type I and II IIPV were highest with tidal versus non-tidal small-FV therapies, particularly in the absence of appropriate accommodation with cycler programming. Setting total UF to zero or too low of a value to meet the patient's actual UF requirements in tidal PD was the most predominant factor associated with IIPV. This clinician-programming situation was present in 25% of all tidal therapies. Studies have shown that UF occurs even when 1.5% dextrose solutions are used over the relatively short dwell times used with APD (21, 22). Failure of the clinician to accommodate for drainage of the "per cycle" UF in addition to the tidal volume itself during programming will logically result in a progressive

accumulation of fluid in the peritoneal cavity, thus increasing IIPV event rates in the latter cycles. Notably, appropriate estimation and programming of total UF, even to within $\geq 50\%$ of the actual UF obtained during TPD, attenuated Level I IIPV events and completely eliminated Level II IIPV events.

Other important factors associated with IIPV include suboptimal and/or inappropriately programmed low drain volume settings (setting I-Drain alarms to $< 70\%$ of the last FV, or setting MDV% for non-I-drain cycles to $< 85\%$ of the FV in standard-FV therapy). Our analysis also clearly demonstrated that larger UF volumes were associated with a profound increase in the rate of IIPV events for both FV therapies, irrespective of the use of a last fill. While we did not do an analysis to examine the interaction between these factors, programming cyclers alarms to allow lower effluent drain volumes would be expected to increase the odds of accumulating residual peritoneal volumes, particularly at higher total therapy UF volumes.

Performing a last manual drain would also be expected to reduce IIPV occurrence rates. However, the data did not bear this out. Conversely, the OR for a Level I IIPV event was actually higher when the LMD was enabled. This apparent paradox might reflect selection of LMD by a clinician recognizing either poor catheter function and drainage or insufficient programming of a target UF. It is conceivable that the clinicians might have improperly relied on LMD to protect patients from an IIPV event. Alternatively, a large single-cycle DV occurring as a result of LMD may appear as an IIPV event, while actually preventing it. Importantly, drainage of this remaining fluid using a LMD reduces both the residual intraperitoneal volume and IPP. LMD should therefore decrease the susceptibility to complications from increased IPP during the daytime when the patient is upright or sitting, positions that can raise IPP (6,14).

Patient/user actions, such as bypass of I-Drain, were also associated with IIPV events for non-tidal standard-FV and small-FV therapies. For non-tidal PD, bypassing I-drain was only associated with a significant increase in IIPV event rate after a daytime dwell or a “last fill” during standard-FV therapy, or in the absence of a preceding LDVA, irrespective of FV. Conversely, while tidal therapies overall were associated with a greater likelihood of IIPV events, bypass of I-Drain during TPD did not further increase the potential for IIPV. One would anticipate that bypassing the initial drain, thus potentially leaving extra residual volume in the peritoneal cavity, would increase the likelihood of IIPV for patients on both tidal and non-tidal therapies. The fact that it did not suggests the possibility of differences in reasons for bypassing between those on tidal versus non-tidal therapies.

While TPD can be programmed in the setting of sub-optimal catheter function, pocketing of dialysate effluent, prolonged effluent drain times, and LDVAs (23), it is primarily prescribed to avoid catheter-related drain pain (24). We would presume that drain pain was the primary reason for tidal programming in our population. An intentional increase in the RV within the peritoneal cavity by TPD serves as a buffer between the PD catheter and the peritoneal membrane covering the visceral organs of the pelvis. Patients doing TPD for drain pain would also be more likely to bypass I-drain to maintain this fluid buffer, again to avoid catheter-peritoneal interaction and drain pain. According to our data, a minority of TPD patients bypassed I-drain (30.4% and 42.3% of standard-FV and small-FV therapies, respectively). The fact that this action did not increase IIPV event rates in TPD patients, irrespective of the presence or absence of a daytime dwell, suggests that these patients learned to bypass in the late stages of I-drain with a relatively empty peritoneal cavity or perhaps only a “tidal percentage” of RV left in the peritoneal cavity.

Conversely, patients on non-tidal PD and using a daytime dwell may have bypassed I-Drain in earlier stages because of sluggish catheter flows and/or impatience to move on with their nighttime therapy, thus leaving larger RVs of dialysate effluent behind. This would increase the association with an IIPV event. The LDVA would not necessarily be triggered in this setting as long as drain flow remained above a minimum value.

Small-FV therapies were assumed to reflect use primarily in young children. These were associated with a higher rate of IIPV and drain-phase bypasses in both tidal and non-tidal therapies. It is possible that the increased frequency of IIPV events was related to the use of more frequent cycles in this population (25). This could result in progressive RV accumulation within the peritoneal cavity, enhancing the probability of IIPV, particularly in the presence of suboptimal PD catheter drainage.

The results of the present analysis provide insight into opportunities to reduce IIPV occurrence rates. Key interventions include appropriate programming of APD cycler settings to meet the patient’s physiologic requirements, and careful patient instruction regarding bypass during either the initial drain or night drains. Bypassing should be avoided until an acceptable RV within the peritoneal cavity has been reached or a LDVA received. This would seem particularly advisable during initial drain, which precedes delivery of multiple PD exchanges provided over a relatively short time interval by the cycler. The latter is critical in patients with relatively large total UF volumes that could result in IIPV, especially in the presence of insufficient PD catheter drainage. PD catheter

dysfunction can also be associated with pocketing of peritoneal fluid, undesirably large RVs, and LDVAs (24–28). LDVAs should prompt patient repositioning to mobilize and drain trapped effluent.

Finally, care must be used when programming total UF for tidal PD. Appropriate total UF programming enables theycler to drain per-cycle UF during the partial drain cycles. While it would be ideal to program total UF in TPD as accurately as possible to decrease progressive accumulation of fluid in the peritoneal cavity, our analysis demonstrated that IIPV events could be reduced or eliminated as long as the programmed total UF was within 50% of the actual UF obtained on theycler.

This study, as well as our previous study (15), highlights the clinical value of achieving the lowest possible intraperitoneal RV before proceeding to the next fill phase of PD cycle. An appropriately functioning PD catheter is inherent to this goal and is of critical importance in ensuring good peritoneal emptying, and reducing pelvic drain discomfort (24). The latter not only impacts quality of life, but is a primary reason for TPD, a critical factor associated with IIPV in this analysis. It is quite possible that the association between TPD and IIPV is not causal, but rather that both are common consequences of a poorly functioning catheter. Indeed, PD catheter malpositioning may be the central factor leading to both prescriber programming changes and patient/user actions leading to IIPV.

Several limitations of our study exist. We did not link DLFs with potential clinical scenarios in this analysis. Based on our previous study (15), clinical experience of the authors (BC, ID, JS) and data from the literature, it is probable that the majority of Level I IIPV events were asymptomatic or associated with minimal clinical symptoms (17,18,28). Our study also only assessed data from the US. It would be interesting to evaluate IIPV event rates from Europe where TPD appears more prevalent (16,29). Finally, a single DLF may reflect multiple IIPV events for the same patient.

CONCLUSION

In conclusion, our study revealed that improper and/or suboptimal cyler programming, primarily related to inadequate total UF estimation with tidal PD, predisposes patients to unintended IIPV events. Furthermore, patient/user drain bypass without reaching target drain volumes may contribute to IIPV events in non-TPD therapies. The association between TPD as well as higher UF volumes and an increased rate of IIPV events suggests the critical importance of optimizing PD catheter function and advising patients against a practice of bypassing drains,

especially in the absence of a LVDA. Our results imply that it is essential that healthcare practitioners caring for PD patients be educated regarding these factors and adjust each patient's APD therapy regimens accordingly to minimize the potential for unintended IIPV events. Further study is warranted to evaluate the association between IIPV events with clinical presentations.

ACKNOWLEDGMENTS

We thank Jay Burkholder from DEKA R&D for detailed review of the manuscript and both Dr. Sarah Prichard and Rona McGreevy for the support and final review of the manuscript.

DISCLOSURES

BC, ID, AB, JM, GP, AK and JS are employees of Baxter Healthcare Corporation and own company stock. SL is the President of SIM Solutions, consults for Baxter Healthcare Corporation, and owns Baxter stock. BB is the President of Lakefront Consulting and consults for Baxter Healthcare Corporation.

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