Haemodynamics in children with a Fontan circulation: effects of afterload reduction

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Chapter 8

Treatment and outcome of plastic bronchitis in single ventricle patients: a systematic review

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Abstract

Plastic bronchitis (PB) is a life-threatening complication in single ventricle (SV) patients of which the exact pathophysiology, outcome and optimal treatment are still unclear. This study aims to systematically review the literature to give insight into the characteristics, outcome and management options of SV patients with PB. A systematic review was conducted, using the electronic database PubMed to find records published up to August 2018, describing SV patients and PB in which characteristics, treatment and/or outcome were adequately described per case. A total of 577 records were screened of which 73 had sufficient data describing 133 SV cases with PB. Most cases had completed a Fontan palliation (*n* = 126) with a median interval between Fontan completion and diagnosis of PB of 18.4 months (Q1-Q3 5.0-36.3). Overall mortality was 15.2% and was associated with diagnosis of PB within 12 months after Fontan palliation (5-year survival of 56.1% ≤12 months vs 94.8% >12 months, *P* = 0.002) and a higher age at Fontan completion (47.4 months for non-survivors vs 36.0 months for survivors, *P* = 0.015). Most patients received a combination therapy from 3 different treatment strategies, i.e. therapy for relief of airway obstruction, anti-inflammatory treatment and treatment to improve haemodynamics of the Fontan physiology (55.1%). In conclusion, SV patients who are diagnosed with PB within 12 months after Fontan palliation have a higher risk of mortality. Moreover, most cases received a combination therapy consisting of all 3 treatment strategies.

Introduction

Plastic bronchitis (PB) is a rare and life-threatening condition characterized by the formation of mucofibrinous casts within the tracheobronchial tree leading to airway obstruction and potentially asphyxia. PB has been described as a complication of respiratory disorders, lymphatic abnormalities and infections but particularly occurs in patients with a single ventricle (SV) after Fontan palliation (1) in which the prevalence has been estimated to be 2-8% (2-4). However, literature describing PB in Fontan patients usually consists of case reports and case series. As a result, knowledge of patient characteristics, survival and possible factors associated with disease outcome is limited. PB has a multifactorial pathogenesis, in which genetic and environmental factors, inflammation and the Fontan physiology itself, with elevated systemic venous pressure, seem to play an important role (5). There is a wide range of therapeutic strategies of which no specific regimen has proven to be consistently effective. A better understanding of SV patients with PB and all therapeutic options is important to recognize patients at risk and improve treatment strategies.

This study aims to systematically review the literature to give insight into the characteristics and outcome of patients with PB after SV palliation, as well as the therapeutic options to treat PB. Furthermore, a case report is presented to illustrate treatment options.

Case report

A boy born with tricuspid atresia and ventricular septal defect received an atrioseptectomy, banding of the main pulmonary artery and bidirectional Glenn anastomosis at the age of 3 months without complication. At the age of 4 years, there were low pulmonary artery pressures post-Glenn (11-12 mmHg) and good left ventricular function. Therefore, the patient received an extracardiac total cavopulmonary connection with a fenestration and division of the main pulmonary artery. The age at which the Fontan operation was performed is in concordance with our institutional standards (6). At the age of 6, 9 months after fenestration closure with an Amplatzer septal device, the patient developed PB with episodes of respiratory distress and daily coughing up large casts.

Diagnostic evaluation showed normal cardiac function, an unobstructed cavopulmonary circuit with a mean pressure of 15-17 mmHg, absence of aortopulmonary collaterals and a mild asymptomatic sinus node dysfunction with

a nodal escape rhythm of 75 beats per minute. There appeared to be a relation between the onset of PB and the fenestration closure. Because of recurrent life-threatening episodes, despite therapy with salbutamol and hypertonic saline, there was opted for an aggressive approach by lowering the pulmonary artery pressure by a Fontan takedown in combination with atrial pacing. The Fontan takedown consisted of removal of the entire extracardiac conduit, reconnection of the inferior caval vein to the right atrium and placement of a central aortopulmonary shunt to improve saturation. Furthermore, for atrial pacing a pacemaker system (A*trial-pacing Atrial-sensing Inhibited-response Rate-adaptive (AAIR)*) was implanted.

Postoperative treatment consisted of azithromycin, a medium-chain triglyceride diet and nebulization with mucolytics, bronchodilators and beclomethasone. Postoperatively, bronchoscopy was necessary to remove a large cast (Figure. 1) and sildenafil, bosentan and nebulization with alteplase were added. Eventually, symptoms of PB ceased and all medications were successfully weaned without recurrence. Due to severe cyanosis and reduced exercise intolerance, it was decided to redo a total cavopulmonary connection with fenestration 4.5 years after Fontan takedown. Haemodynamic assessment before the operation showed low pulmonary artery pressures (6-7 mmHg). Postoperatively, the patient's physical condition improved substantially and currently, >1.5 years post-redo-Fontan completion, he had no recurrence and only receives phenprocoumon and azithromycin.

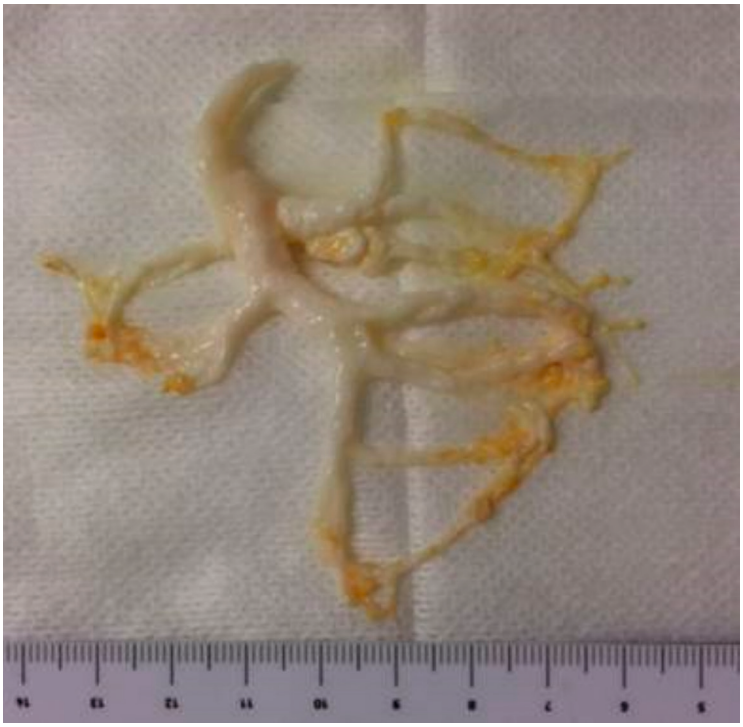

Figure 1. Expectorated bronchial cast

Materials and Methods

A systematic review of published studies describing SV patients with PB was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement protocol (7). The PubMed database was used to search relevant records published up to August 2018, date of search 13 August 2018 (Figure 2). The following search terms were used: plastic bronchitis OR bronchial cast OR bronchial casts. The search was performed by the primary author (L.M.H.).

Titles and abstracts were screened and selected based on the following predefined criteria: the entire or partial study population consisting of SV patients who were diagnosed or treated for PB and characteristics, treatment and/or outcome being well described per case. All full-text records were studied, and non-English records were excluded. The case presented by our own centre was also included.

The following data were extracted: publication year, number of SV cases with PB and per case gender, type SV, type palliation, age at PB diagnosis, age at Glenn or Fontan

operation, follow-up time after diagnosis, history of chylothorax or protein-losing enteropathy (PLE), treatment received and outcome after treatment. Therapeutic options were divided into relief of airway obstruction, anti-inflammatory treatment and treatment improving haemodynamics of the Fontan physiology. Furthermore, characteristics between patients who survived or died were compared as well as survival between patients diagnosed within or after 12 months after Fontan completion.

Statistical analyses

Categorical data were extracted per case based on the presence or absence of a certain variable. Regarding the continuous data, all available data per individual case were directly extrapolated from the article. Although most articles provided data per individual case, a few articles only provided data on a group level. For those articles we had to make assumptions and therefore we used the available median of the entire group that was described in the article. This was necessary for 9 cases and only for the follow-up time since diagnosis of PB. Moreover, for 1 article we had to use 2 medians' to extract the necessary data for 2 cases (8). Data are presented as numbers with percentages for categorical data and median with first to third quartiles (Q1-Q3) for continuous data. To determine risk factors for negative outcome, continuous data were analysed using the Mann-Whitney *U*-test and categorical data using the Fisher's exact test. Kaplan-Meier curves were conducted to present overall survival and to compare the difference in survival between patients who were diagnosed with PB within or after 12 months after Fontan completion using the log-rank test.

SPSS (version 23) software was used. A *P*-value of 0.05 or less was considered statistically significant.

Results

Of the 577 records found in PubMed, 88 contained titles and abstracts that met the inclusion criteria. After studying the records in full text, 73 describing 133 PB cases were included in the review (Figure. 2). Fifty-three records consisted of a single case report, 18 records consisted of small case series and 2 records consisted of larger case series (see Supplementary Material, *Table S1*).

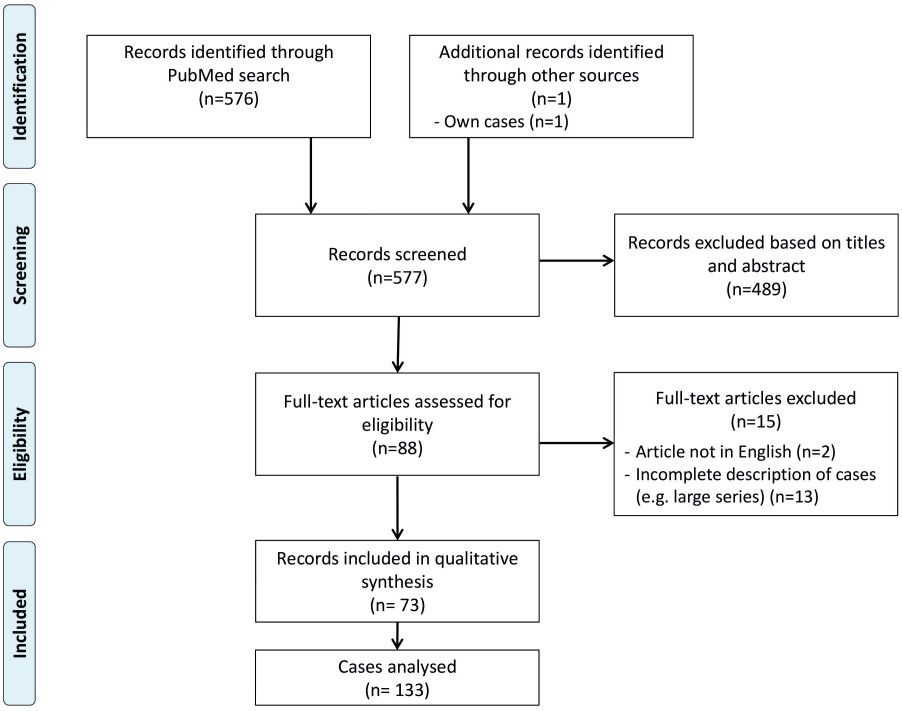

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of search results.

Patients characteristics are described in Table 1. Most cases were diagnosed with PB after Fontan palliation (*n* = 126) with a median age at the diagnosis of 60.0 months and the median time from Fontan to diagnosis of 18.4 months. Seven patients had a bidirectional Glenn anastomosis at the time of diagnosis. The median follow-up time after diagnoses was 18.0 months. After diagnosis, 10 cases needed extracorporeal membrane oxygenation support of which 2 eventually died. Overall mortality was 15.2% with a 5-year survival of 77.4% (Figure. 3). Furthermore, mortality seemed to have decreased over time as the mortality rate in articles published before 2012 was found to be 24.4% compared to 10.5% in articles published between 2012 and 2018. The median time to death after diagnosis was 3.5 months. Resolution of PB occurred in 51.5%, with 26.8% still experiencing symptoms at the end of follow-up.

Table 1. Characteristics and outcome of cases

Variables	
Sex (*n* = 104)	
Male	66 (63.5)
Female	38 (36.5)
Type single ventricle (*n* = 104)	
Single left ventricle	51 (49.0)
Single right ventricle	53 (51.0)
Type palliation (*n* = 133)	
Fontan	126 (94.7)
Glenn	6 (4.5)
Hemi-Fontan	1 (0.8)
Age at diagnosis of PB (*n* = 112, months)	60.0 (41-83.8)
Age at Glenn operation (*n* = 5, months)	6.0 (5.1-72.5)
Interval between Glenn operation and PB (*n* = 5, months)	12.0 (9.5-64.1)
Age at Fontan operation (*n* = 98, months)	36.6 (25.8-51.5)
Interval between Fontan operation and PB (*n* = 110, months)	18.4 (5-36.3)
Follow-up since diagnosis of PB (*n* = 126, months)	18.0 (6.8-37.1)
History of chylothorax	35 (26.3)
History of or occurrence of PLE alongside PB	6 (4.5)
Patients who received ECMO	10 (7.5)
Outcome at follow-up (*n* = 132)	
Death	20 (15.2)
Alive	112 (84.8)
Symptom free of PB at follow-up	68 (51.5)
Still symptoms of PB at follow-up	30 (22.7)
Unknown	14 (10.6)

All values are expressed as *n* (%) or median (Q1-Q3).
ECMO: Extracorporeal membrane oxygenation; PB: Plastic Bronchitis; PLE: Protein losing enteropathy.

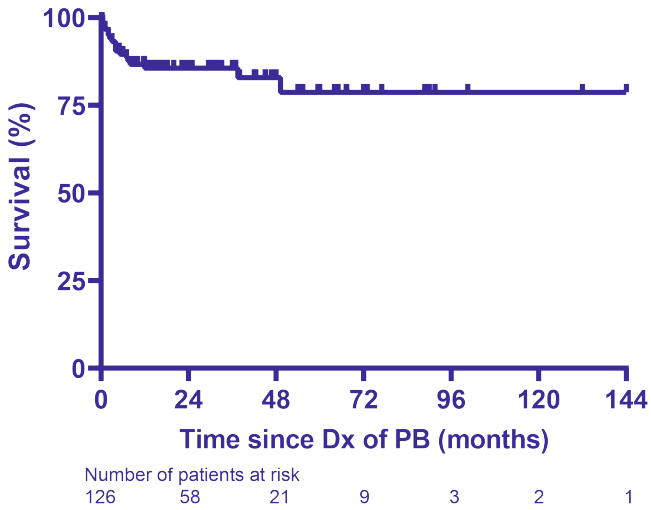

Figure 3. Kaplan–Meier curve of overall survival of Fontan patients after Dx with plastic bronchitis. Dx: diagnosis; PB: plastic bronchitis.

An older age at the time of Fontan operation (Table 2; 47.4 months for non-survivors vs 36.0 months for survivors) and the diagnosis of PB within 12 months after Fontan completion (Figure 4; 5-year survival of 56.1% with diagnosis ≤12 months vs 94.8% >12 months) were associated with an increased risk of mortality.

Table 2. Comparison of the characteristics between patients who survived or died after diagnosis of PB

Characteristics	Alive (n = 113)	Death (n = 20)	P-value
Gender (*n* =104)			1.000
Female	32 (36.4)	6 (37.4)	
Male	56 (63.6)	10 (62.5)	
Type single ventricle (*n* = 104)			1.000
Single left ventricle	45 (49.5)	6 (50.0)	
Single right ventricle	46 (50.5)	6 (50.0)	
Age at diagnosis of PB (*n* = 111, months)	60.0 (39.6-84.0)	55.0 (49.7-90.8)	0.854
Age at Fontan operation (*n* = 97, months)	36.0 (25.0-48.0)	47.4 (42.9-75.0)	0.015
Interval between Fontan operation and PB (*n* = 109, months)	23.9 (6.0-43.2)	6.0 (3.0-12.8)	0.052
History of chylothorax	25 (22.1	9 (45.0)	0.387
History of/or occurrence of PLE alongside PB	5 (4.4)	1 (5.0)	1.000
Patients who received ECMO	7 (6.2)	2 (10.0)	0.279

All values are expressed as n (%) or median (Q1-Q3).

ECMO: Extracorporeal membrane oxygenation; PB: Plastic Bronchitis; PLE: Protein-losing enteropathy.

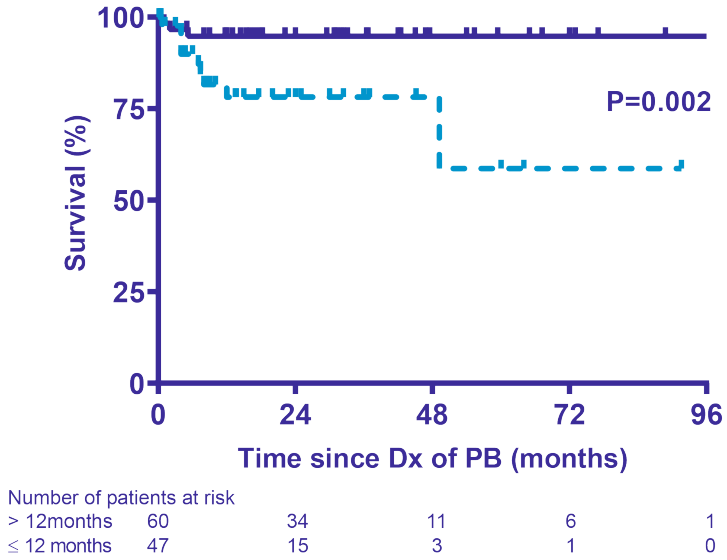

Figure 4. Kaplan–Meier curve of survival of Fontan patients after Dx with plastic bronchitis based on period of Dx after Fontan palliation, Dx within 12 months (light blue dotted line) and after 12 months (dark blue solid line) after Fontan palliation. The P-value of the log-rank test between groups is indicated in the graph. Dx: diagnosis; PB: plastic bronchitis.

Treatments were divided into 3 different treatment strategies (Table 3): (i) therapy for relief of airway obstruction, (ii) anti-inflammatory treatment and (iii) treatment improving the haemodynamics of the Fontan physiology. Most patients received a combination therapy from all 3 different treatment strategies (55.1%). In 6 patients treatment was not defined. Relief of airway obstruction was the most frequently reported strategy (91.3%), especially during the acute phase of PB. More than 50% of the patients received a combination of different aerosolized drugs for cast relief. Anti-inflammatory therapy was the least frequently reported (65.4%). Therapy improving haemodynamics was variable and consisted of optimizing the Fontan circulation or cardiac function (61.4%), antiarrhythmic therapy (8.7%), inhibition of lymph leakage/production (33.1%), decompression of the Fontan circulation (23.6%) and heart transplantation (9.4%).

Table 3. Description of therapeutic options applied for treatment of PB

	Total (n =127)
Relief of airway obstruction	116 (91.3)
Bronchoscopic cast extraction	62 (48.8)
Chest physiotherapy	31 (24.4)
Mechanical ventilation therapy	6 (4.7)
Fibrinolytics (total)	75 (59.1)
Tissue plasminogen activator/ Urokinase	70 (55.1)
Nebulized heparin	10 (7.9)
Mucolytics (total)	73 (57.5)
Bronchodilators	76 (59.8)
Anti-inflammatory	83 (65.4)
Corticosteroids	74 (58.3)
Antibiotics	37 (29.1)
Haemodynamics (CO/CVP/Lymph)	102 (80.3)
Optimizing Fontan circulation or cardiac function	78 (61.4)
Fontan conversion	1 (0.8)
Fontan revision	2 (1.6)
Surgical or interventional relief of Fontan circuit obstruction	25 (19.7)
Valve replacement	2 (1.6)
Ligation/embolization of aortopulmonary collaterals	17 (13.4)
Pulmonary vasodilators (total)	57 (44.9)
Bosentan	18 (14.2)
Sildenafil	54 (42.5)
Systemic prostacyclin	2 (1.6)
Heart failure therapy/medication	22 (17.3)
Anti-arrhythmic therapy	11 (8.7)
Pacemaker therapy	9 (7.1)
Ablation	1 (0.8)
Antiarrhythmic agents	1 (0.8)
Inhibition of lymph leakage/production	42 (33.1)
Low fat diet	13 (10.2)
Octreotide	1 (0.8)
Ligation/embolization of thoracic duct or lymphatic vessels	33 (26.0)
Decompression of Fontan circulation	30 (23.6)
Creation, dilation or stenting of fenestration	24 (18.9)
Takedown of Fontan circulation	6 (4.7)
Heart transplantation	12 (9.4)

All n (%) values represent number of cases in which the value was described. CO: cardiac output; CVP: central venous pressure; PB: Plastic bronchitis.

Discussion

PB is a rare complication in SV patients. Through collecting all available SV cases, we were able to describe characteristics, survival and therapy of 133 cases. Major findings include an overall mortality of 15.2%, diagnosis within 12 months after Fontan palliation and a higher age at Fontan operation, both of which are associated with increased risk of mortality. Moreover, the majority of cases received a combination therapy consisting of all 3 treatment strategies.

Mortality in this review was considerably lower compared to previous reports. A case-control study reported an overall mortality of 32.0% in Fontan patients diagnosed before 2012 (9). If we compare mortality within our review, mortality is higher in cases published before 2012 which may imply improving survival. Moreover, recent studies of PLE in Fontan patients also reported improved survival (10). Nevertheless, these higher survivals could be caused by improvement in the survival of all Fontan patients. Furthermore, mortality of PLE is higher (26.0-40.0%) (6, 10) and resolution after treatment much lower (31%)(6) when compared to PB (51.5%). Although both diseases share a similar pathological basis, PB is an acute disease that typically appears shortly after Fontan operation while PLE typically appears in a more chronic fashion several years after operation (6, 10).

One study reported that an earlier onset of PB after the Fontan palliation was associated with a higher risk of mortality (9), a risk factor we also found. However, early onset of PB may be a manifestation of a poor Fontan circulation and may therefore be correlated with an increased risk of death. Furthermore, we found an older age at Fontan operation as an additional risk factor. Whether this finding has been influenced by other factors could not be determined. For example, patients may have been operated late because they were suboptimal Fontan candidates. Nevertheless, it seems to be in line with most series that older age at Fontan operation is an independent risk factor for poor outcome (11-13). Other variables of interest for mortality, such as elevated Fontan pressures and ventricular function, or possible risk factors for the development of PB, could not be analysed in our study. In our case, the onset of PB seemed to be related to an elevated Fontan pressure after fenestration closure.

Treatment

We divided treatments into 3 therapeutic strategies including relief of airway obstruction, anti-inflammatory treatment and treatment improving haemodynamics of the Fontan physiology. Most patients described in the literature, including our

case, received a combination of all treatment strategies, which eventually led to the successful management of PB in the majority of cases. Therefore, based on all cases included in this systematic review, we developed a treatment algorithm in which treatment after the acute phase consists of a combination of all 3 different treatment strategies (Figure 5).

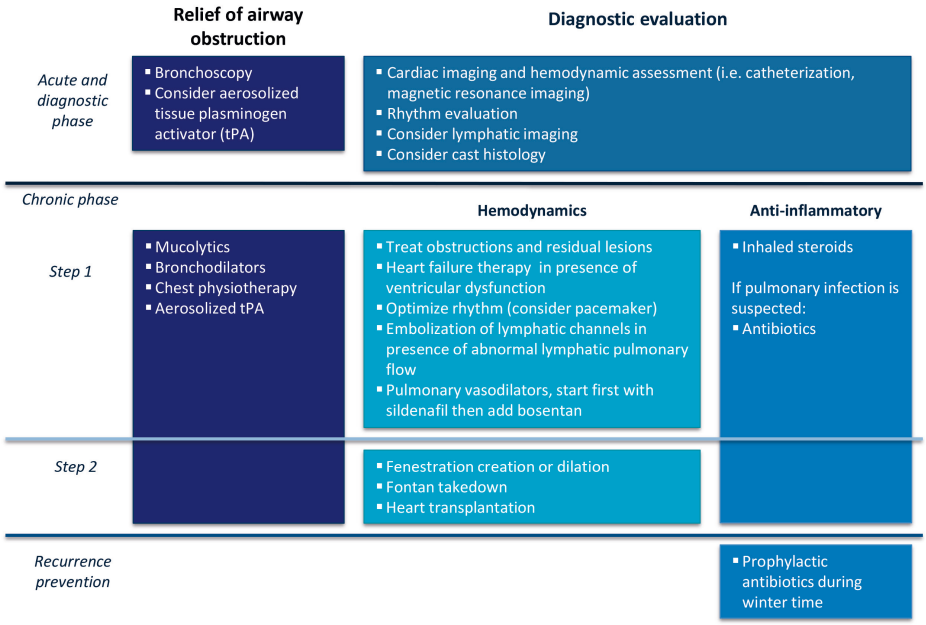

Figure 5. Treatment algorithm for Fontan patients diagnosed with plastic bronchitis. tPA: tissue plasminogen activator.

Relief of airway obstruction

In emergency cases, immediate bronchoscopy should be considered. However, complete lavage is not always possible as casts are often fragile. Alternatively, mechanical ventilation with positive–negative pressure (14-17) or high frequency jet ventilation (18) can be used for cast relief. However, a need for high airway pressure and repeated bronchoscopies should be avoided as both will decrease passive blood flow through the pulmonary system, negatively affecting the cardiac output of Fontan patients (19). With the absence of acute respiratory failure, treatment with chest physiotherapy, bronchodilators, mucolytics and fibrinolytics can be initiated to enhance cast expectoration or to induce the lysis of casts. Inhalation of plasminogen activator, a fibrinolytic, has proven to be an effective and safe treatment for cast

reduction (20-23), acute exacerbations (24) and chronic therapy in preventing cast formation (21, 25). Although all these therapies may be effective for cast relief, they are not able to prevent recurrence.

Anti-inflammatory treatment

Because some casts consist of inflammatory cells (21, 26) and since there is a relation between PB and acute respiratory infections (2), anti-inflammatory treatment has been frequently used. This most often consists of inhaled corticosteroids and antibiotic treatment. Yet, evidence of effectiveness of steroids is limited. However, a case with acellular casts resolution appeared after the introduction of corticosteroids (27) and another case remained cast free while chronically on steroid treatment (26). Inhaled steroids may be effective as it is believed that altered Fontan haemodynamics cause mucosal injury inducing mild airway inflammation. Furthermore, as cast recurrence has been associated with respiratory infections (21), prophylactic antibiotic treatment may be a useful adjunct therapy for recurrence prevention, as shown in our case and another case report (28).

Therapy improving the Fontan circulation

The Fontan physiology itself also contributes to the development of PB. A lower cardiac output, elevated systemic venous pressure and abnormal lymphatic flow may contribute (5). Therefore, a thorough diagnostic evaluation of the Fontan circulation is essential to determine a therapeutic strategy. Nevertheless, the onset of PB can occur in Fontan patients with relative normal Fontan pressures with preserved cardiac function without residual lesions (21, 26).

Relief or repair of residual lesions and obstructions have to be considered. Resolution of PB has been reported after successful interventions for ventricular, arterial and venous obstruction atrioventricular valve regurgitation and aorta-pulmonary collaterals (21). Although these results are promising, not every intervention in each individual will lead to successful treatment (5, 29, 30). In addition, medical therapies may also improve haemodynamics and optimize the circulation. Pulmonary vasodilators, sildenafil and bosentan in particular have shown to be an effective and safe treatment that can be administered chronically (21, 26, 31-33).

Improvement in cardiac output can be obtained by antiarrhythmic therapy. Atrial pacing may restore chronotropic incompetence and atrioventricular synchrony but has only led to the resolution of PB in some cases (1, 34, 35), while others report less favourable results (5, 23, 25, 36, 37).

Inhibition of lymph production or leakage could be an effective therapy, especially in those who previously had a chylothorax or currently have chylous casts. A low-fat or medium-chain triglyceride diet has proven to be successful (37, 38). However, recurrence can occur when the diet is stopped (37). Furthermore, interruption of lymphatic flow through embolization or ligation has shown to improve symptoms and even temporarily resolution (26). However, not all patients have abnormal lymphatic flow (26). Therefore, lymphatic imaging should ideally be part of the diagnostic evaluation.

If the Fontan circulation cannot be further optimized, then decompression should be considered. A Fontan takedown to a Glenn physiology as well as fenestration of the Fontan pathway can result in reduced venous pressures and improved cardiac output. However, both therapies have shown various effects, with results ranging from no effect (39-41) to the improvement of symptoms (21, 26, 31, 39, 42) or even complete resolution (21, 36, 43-46). Although catheter-created fenestration is the least invasive method, the chance of spontaneous closure is high (36). Furthermore, when surgery is considered, a takedown will have the largest effect on lowering venous pressures and improving cardiac output but also will result in significant cyanosis, which can be a complicating factor if PB persists. In our case, the severe PB, which developed after fenestration closure, resolved after temporary Fontan takedown and appeared to be a successful therapy by drastically decreasing the pulmonary circulation. After the resolution of casts and a long recovery period, re-Fontan procedure with a relatively large fenestration was feasible without PB recurrence.

Besides improving the hemodynamic of the Fontan circulation itself, a heart transplantation could be considered in some cases. Although Fontan patients with PB have a high mortality peri-transplantation (47, 48), long-term mortality is comparable to the general paediatric heart transplant population (47). As residual casts may be present, airway clearance during and early after transplantation is necessary to reduce postoperative morbidity (49, 50). Cardiac transplantation could be very successful for treating PB, as in a large group of Fontan patients with PLE resolution occurred in almost all cases after heart transplantation (51).

Limitations

This review includes only patients already diagnosed with PB, and therefore we could not identify risk factors for PB itself. Furthermore, missing data and reporting bias were present due to the inclusion of case reports. For example, we were not

able to report the type of Fontan operation performed. Potential risk factors such as haemodynamic measurements of cardiac catheterization could not be studied, as they were only infrequently reported in the cases. Due to the possible presence of publication bias, the study population may also not be representative of the total population of Fontan patients with PB. However, missing data and reporting bias may have biased results in both directions. Finally, due to the many therapy types, it was only possible to provide an overview instead of an analysis of different therapeutic strategies.

Conclusion

Most SV patients with PB are diagnosed early after the Fontan operation with approximately one-sixth dying shortly after diagnosis. Furthermore, diagnosis of PB within 12 months after Fontan palliation and a higher age at Fontan operation are associated with an increased risk of mortality. Whether these findings are independent predictors for mortality could not be investigated. Although treatments varied enormously and none has proven to be consistently effective, this study together with our own experience suggests that therapy of PB consisting of relief of airway obstruction, anti-inflammatory treatment and treatment improving haemodynamics of the Fontan physiology can be an effective strategy to cure PB. In addition, a temporary Fontan takedown could be a life-saving therapy. During this period, PB can resolve, pulmonary circulation can recover and the Fontan circulation could be restored successfully at a later time. Nevertheless, large multicentre cohort studies are warranted to unravel the exact pathophysiology to determine which patients are at risk for developing PB and which therapeutic strategy is most effective.

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Supplementary materials

Table S1. Overview of included records

Study	N cases	Age at diagnosis of PB	Interval Fontan operation until PB	Follow-up since diagnosis of PB	Outcome	Therapy										
						Symptomatic cast relief		Anti-inflammatory-treatment			Hemodynamics (CO/CVP/Lymph)					
		median (min-max) months	median (min-max) months	median (min-max) months	Died (N cases)	Y/N	N cases	Y/N	N cases	Y/N	N cases Tot	Opt	Rhyt	Lymp	Dec	HTx
Okada et al. 2018 [16]	1	192	171	0,5		Yes	1	Yes	1	No						
DePopas et al. 2017 [41]	3	60 (72-108)	24 (24-48)	45 (42.5-73)		Yes	3	No		Yes	3	1	1	2	1	
Parent et al. 2017 [50]	3	-	-	54 (48-90)		Yes	3	Yes	3	Yes	3			1		3
Perez Ruiz et al. 2017 [52]	1	17	-	1	1	Yes	1	No		No						
Unseld et al. 2017 [8]	4	50.4 (39.6-61.2)	15.6 (4.8-27.6)	58.2 (12-88.8)	2	ND		ND		ND						
Charlagorla et al. 2016 [43]	1	60	30	24		Yes	1	Yes	1	Yes	1				1	
Dori et al. 2016 [26]	16	65.6 (20.8-136.6)	20.6 (0-51.6)	32.2 (13.7-100.6)	1	Yes	15	Yes	13	Yes	16	16	1	15	3	1
Guevara et al. 2016 [53]	1	-	-	-		Yes	1	No		Yes	1			1		
Ugaki et al. 2016 [29]	1	51	3	8	1	Yes	1	No		Yes	1	1		1	1	
Wesnerowicz et al. 2016 [45]	2	79.8 (21-138.5)	52.8 (9-96.5)	26.8 (24-29.5)		Yes	2	Yes	1	Yes	2	2			1	
Chung et al. 2015 [54]	1	60	51	65		Yes	1	No		Yes	1			1		
Hallbergson et al. 2015 [39]	2	84 (38.4-129.6)	2.9 (0.8-5)	14 (4-24)	1	No		No		Yes	2				2	

Table S1. Overview of included records (continued)

Study	N cases	Age at diagnosis of PB median (min-max) months	Interval Fontan operation until PB median (min-max) months	Follow-up since diagnosis of PB median (min-max) months	Outcome Died (N cases)	Therapy										
						Symptomatic cast relief		Anti-inflammatory-treatment			Hemodynamics (CO/CVP/Lymph) N cases					
						Y/N	N cases	Y/N	N cases	Y/N	Tot	Opt	Rhyt	Lymp	Dec	HTx
Jasinovic et al. 2015 [55]	2	66.5 (56-77)	-	20.5 (3-38)	1	Yes	2	No		No						
Singhi et al. 2015 [56]	1	62	2	9		No		No		Yes	1	1				
Tanase et al. 2015 [38]	4	29 (21.5-45)	10 (0.5-24)	10.8 (5-25)		Yes	4	No		Yes	4	4		4		
Avitable et al. 2014 [21]	14	-	18.0 (0.3-184.8) (1 Missing)	32.4 (3-54)		Yes	14	Yes	14	Yes	14	14		1	7	3
Colaneri et al. 2014 [24]	1	156	84	12		Yes	1	Yes	1	Yes	1	1				
Dori et al. 2014 [57]	1	68	32	11,7		Yes	1	Yes	1	Yes	1	1		1		
Eason et al. 2014 [58]	1	60	24	12		Yes	1	Yes	1	Yes	1	1				
Lis et al.; 2014 [59]	1	18	-	1,1		Yes	1	Yes	1	Yes	1	1				
Parent et al. 2014 [49]	1	-	-	-		Yes	1	No		Yes	1			1		1
Brooks et al. 2013 [15]	2	54.0 (41-66.9)	36.5 (24-48.9)	132 (1 Missing)		Yes	2	Yes	1	No						
Ezmigna et al. 2013 [60]	1	72	24	15.4		Yes	1	Yes	1	Yes	1			1		
Grutter et al. 2013 [61]	1	144	60	18		Yes	1	Yes	1	Yes	1	1				
Kobayashi et al. 2013 [40]	1	42	6	8		Yes	1	Yes	1	Yes	1	1			1	
Kunder et al. 2013 [46]	4	33 (24-36)	1 (3 Missing)	7.5 (3-144)		Yes	4	Yes	4	Yes	3	2			2	
Lubcke et al. 2013 [23]	1	144	120	9		Yes	1	Yes	1	Yes	1		1			
Singhal et al. 2013 [62]	2	101.5 (83-120)	65.5 (35-96)	7.5 (2-13)		Yes	2	Yes	1	Yes	2	2		1	1	
Do et al. 2012 [42]	1	132	72	9		Yes	1	Yes	1	Yes	1	1			1	

Table S1. Overview of included records (continued)

Study	N cases	Age at diagnosis of PB median (min-max) months	Interval Fontan operation until PB median (min-max) months	Follow-up since diagnosis of PB median (min-max) months	Outcome Died (N cases)	Therapy											
						Symptomatic cast relief		Anti-inflammatory-treatment		Hemodynamics (CO/CVP/Lymph)							
											N cases						
						Y/N	N cases	Y/N	N cases	Y/N	Tot	Opt	Rhyt	Lymp	Dec	HTx
Elahi et al. 2012 [63]	1	48	6	0,33		Yes	1	No		No						
Grutter et al. 2012 [64]	4	43 (25-54)	4 (0-10)	7 (0-10)	2	Yes	4	Yes	4	Yes	4	4				
Kovesi et al. 2012 [65]	1	13	-	67,4		Yes	1	Yes	1	Yes	1	1				
Larue et al. 2012 [5]	2	121 (38-204)	79 (2-156)	36 (30-42)		Yes	2	Yes	2	Yes	2	2	1		1	1
Nawa et al. 2012 [66]	1	96	60	1		Yes	1	No		Yes	1	1				
Parikh et al. 2012 [37]	1	132	110	72		Yes	1	Yes	1	Yes	1	1	1	1		
Wirbelauer et al. 2012 [67]	1	60	36	24		Yes	1	No		Yes	1	1		1		
Elmallah et al. 2011 [14]	1	72	-	42		Yes	1	Yes	1	Yes	1					1
Laubisch et al. 2011 [68]	1	48	24	32		Yes	1	Yes	1	Yes	1	1				1
Silva et al. 2011 [69]	1	60	-	2,4	1	Yes	1	Yes	1	Yes	1				1	
Guimaraes et al. 2010 [70]	1	54	14	3		Yes	1	No		Yes	1	1				
Preciado et al. 2010 [19]	3	36 (8-36)	6 (2 Missing)	2 (0-4.7)	1	Yes	3	Yes	2	No						
Reinhardt et al. 2010 [31]	4	117.6 (81.6-148.8) (1 missing)	78 (42-96) (1 missing)	21.4 (12-30.8) (2 missing)		No		No		Yes	4	4			3	1
Do et al. 2009 [22]	1	68	2	1		Yes	1	No		Yes	1	1		1		
Zahorec et al. 2009 [18]	2	127.4 (74-180.8)	1.4 (0.8-2)	32 (4-60)	1	Yes	2	Yes	1	No						
Cajaiba et al. 2008 [71]	1	192	144	0,16	1	Yes	1	No		No						

Table S1. Overview of included records (continued)

Study	N cases	Age at diagnosis of PB median (min-max) months	Interval Fontan operation until PB median (min-max) months	Follow-up since diagnosis of PB median (min-max) months	Outcome	Therapy										
						Symptomatic cast relief		Anti-inflammatory-treatment			Hemodynamics (CO/CVP/Lymph) N cases					
					Died (N cases)	Y/N	N cases	Y/N	N cases	Y/N	Tot	Opt	Rhyt	Lymp	Dec	HTx
Verghese et al. 2008 [72]	1	32	14			Yes	1	No		No						
Zaccagni et al. 2008 [73]	1	180	108	17		Yes	1	No		Yes	1	1				
Nayar et al. 2007 [74]	1	102	15	2	1	Yes	1	Yes	1	Yes	1			1		
Haseyama et al. 2006 [32]	1	38	2	9		No		Yes	1	Yes	1	1				
Apostolopoulou et al. 2005 [33]	1	92	8	91,6		Yes	1	Yes	1	Yes	1	1			1	
Shah et al. 2006 [17]	2	48 (1 Missing)	36 (1 Missing)	14.5 (5-24)		Yes	1	Yes	1	Yes	2			2		
Peleg et al. 2005 [75]	1	75	3	4	1	Yes	1	Yes	1	No						
Tzifa et al. 2005 [76]	1	41	5	8,5		Yes	1	Yes	1	Yes	1	1				
Wakeham et al. 2005 [25]	1	50	35	31		Yes	1	Yes	1	Yes	1	1	1	1		
Wilson et al. 2005 [36]	1	61	1	15		Yes	1	Yes	1	Yes	1		1		1	
Yalcin et al. 2005 [77]	1	90	60	17		Yes	1	No		Yes	1	1				
Barber et al. 2004 [34]	1	54	6	15		Yes	1	No		Yes	1	1	1			
Chaudhari et al.; 2004 [44]	1	42	1	36		Yes	1	Yes	1	Yes	1				1	
Dicindio et al. 2004 [78]	1	28	10	0,46	2	Yes	1	Yes	1	No						
Ishman et al. 2003 [79]	1	60	7	12		Yes	1	No		No						
Onoue et al. 2003 [27]	1	96	60	36,7		Yes	1	Yes	1	No						

Table S1. Overview of included records (continued)

Study	N cases	Age at diagnosis of PB median (min-max) months	Interval Fontan operation until PB median (min-max) months	Follow-up since diagnosis of PB median (min-max) months	Outcome Died (N cases)	Therapy										
						Symptomatic cast relief		Anti-inflammatory-treatment			Hemodynamics (CO/CVP/Lymph) N cases					
						Y/N	N cases	Y/N	N cases	Y/N	Tot	Opt	Rhyt	Lymp	Dec	HTx
Brogan et al. 2002 [1]	1	65	5	20		Yes	1	Yes	1	Yes	1		1	1		
Costello et al. 2002 [80]	1	53	27	5,2		Yes	1	Yes	1	No						
Stiller et al. 2002 [81]	2	57 (42-72)	26.5(17-36)	18 (12-24)		Yes	2	Yes	2	Yes	2	1		2		
Hug et al. 2001 [82]	1	47,4	1,4	0		Yes	1	No		No						
McMahon et al. 2001 [30]	1	30	6	7,4		Yes	1	Yes	1	Yes	1	1				
Setzer et al. 2001 [83]	1	72,2	0,16	0,16	1	Yes	1	No		No						
Quasney et al. 2000 [35]	1	60	24	36,5		Yes	1	Yes	1	Yes	1		1			
Collorodi et al. 1990 [84]	1	84	-	-	1	Yes	1	No		No						
Languepin et al. 1999 [85]	1	24	9	64		Yes	1	Yes	1	Yes	1	1		1		
Seear et al. 1997 [86]	3	96 (60-144)	12 (12-12) 1Missing	0.69 (0.46-1.2)		Yes, 2ND	1	Yes, 2ND	1	No, 2ND						
Bowen et al. 1985 [87]	1	101	5	37	1	No		Yes	1	No						
Own case	1	70	19	77		Yes	1	Yes	1	Yes		1	1	1	1	

CO= Cardiac output; CVP= Central Venous Pressure; Dec= Therapy for decompression of Fontan circulation; HTx= Heart transplantation; Lymp= Therapy for inhibition of lymph leakage/production; N cases = Number of cases; ND = Not defined; Opt= Therapy for optimizing Fontan circulation; Rhyt= Anti-arrhythmic therapy; Y/N= Yes/No.
* Not all variables that were investigated in this systematic review are included in this table.

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