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Review Article

Neonatal Congenital Chylothorax Managed with Octreotide: A Review of Published Cases

Salminen N[1]*, Gallo C[2] and Iliev I[3]

[1]Department of Neonatology, University of Turku, Turku, Finland
[2]Department of Paediatric Surgery, University of Padua, Padua, Italy
[3]Department of Paediatrics, Medical University of Plovdiv, Plovdiv, Bulgaria

*Address for Correspondence: Noora Salminen, Department of Neonatology, University of Turku, Turku, Finland; E-mail: noora.salminen@universityofturku.edu

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Abstract

Background: Congenital chylothorax is a rare accumulation of lymphatic fluid in the pleural space and the most common cause of neonatal pleural effusion, carrying substantial morbidity from pulmonary hypoplasia, hydrops, and secondary immunodeficiency.

Objective: To review published case reports/series, epidemiologic, pathophysiologic and management literature on octreotide (somatostatin-analogue) therapy for congenital chylothorax.

Methods: Narrative review of individually verified case reports, case series, systematic reviews, a Cochrane review, and cohort/epidemiologic studies.

Findings: Incidence estimates range from 1:5,800 to 1:24,000 live births. Across 11 published reports, octreotide (0.5-20 mcg/kg/h intravenous, or 10-70 mcg/kg/day subcutaneous) produced resolution in most treated neonates, including a 14-patient series with 85.7% survival and significantly reduced drainage (P=.002), though a Dutch series and the largest pooled analysis (753 cases) found inconsistent, dose-variable effects and no completed randomized trial.

Conclusions: Octreotide is a reasonable adjunct to conservative management (drainage, medium-chain-triglyceride feeding) in refractory congenital chylothorax, but evidence remains limited to case-level data, and dosing/duration are not standardized.

Keywords: Congenital chylothorax; Octreotide; Somatostatin; Neonate; Pleural effusion

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Introduction

Chylothorax, the accumulation of chyle-laden lymphatic fluid within the pleural space, is the most common cause of pleural effusion in the neonatal period [1]. When it arises without preceding surgery or trauma it is termed congenital (or primary/idiopathic) chylothorax, distinguishing it from postoperative chylothorax after cardiothoracic surgery [2]. Congenital chylothorax can present antenatally as fetal hydrothorax with secondary pulmonary hypoplasia and non-immune hydrops, or postnatally as acute respiratory distress requiring urgent drainage [3,4]. Management is multimodal, combining pleural drainage, nutritional strategies (fasting with parenteral nutrition or medium-chain-triglyceride [MCT]-enriched feeds), and, for refractory cases, pharmacologic therapy with octreotide or somatostatin, pleurodesis, or surgery [3,5]. Since the first published use of octreotide for congenital chylothorax in 2004 [6,7], a growing but still exclusively case-based literature has accumulated, comprising isolated case reports, a handful of small case series, and two systematic reviews that together have never exceeded roughly 90 treated neonates [8]. No randomized controlled trial of octreotide in this population has been completed or is likely feasible given the rarity of the disease, so clinicians must currently base dosing and duration decisions on this heterogeneous, largely retrospective evidence. This review synthesizes the published individual case reports and series of neonatal congenital chylothorax treated with octreotide, alongside the epidemiologic, pathophysiologic, diagnostic and outcome literature that frames their interpretation, with the aim of consolidating practical dosing ranges, expected response rates, and red flags for treatment failure into a single reference for clinicians managing this uncommon condition.

Epidemiology

Congenital chylothorax is rare. A prospective nationwide surveillance study in Germany estimated an incidence of 1:24,000 live births [9], while other single-center and systematic-review estimates place the incidence between 1:5,800 and 1:24,000 [10,11]. The largest published pooled analysis, a systematic review of 753 cases from 157 studies published between 1990 and 2018, found an all-cause mortality of 28%, prematurity in 71% of cases, male predominance (57%), a mean gestational age of 34 weeks, and bilateral disease in 79% [12]. A smaller Australian series of 10 cases over several years likewise found an overall prevalence of less than one case per year at a single

center, with the majority of infants having associated chromosomal anomalies or dysmorphic features [13]. These figures underline both the rarity of the disease and the impossibility, given current data, of an adequately powered randomized trial of any single therapy, octreotide included.

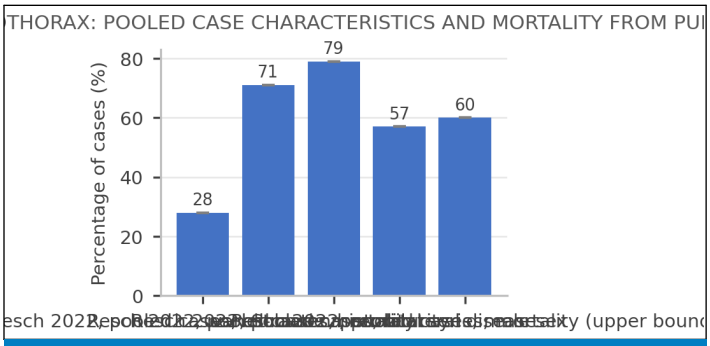

Figure 1: Pooled case characteristics from the largest published systematic analysis of congenital chylothorax (753 cases, 157 studies, 1990-2018): 28% all-case mortality, 71% prematurity, 79% bilateral disease, 57% male sex [12], compared with the upper bound of mortality (60%) reported in an early foundational series [26].

Pathophysiology

Congenital chylothorax most commonly reflects a developmental anomaly of the thoracic duct or pulmonary lymphatics — lymphangiectasia, lymphatic dysplasia, or thoracic duct atresia/obstruction — allowing chyle to leak into the pleural space [4,3]. A minority of cases are associated with recognized genetic or chromosomal syndromes, including Noonan syndrome, Turner syndrome, trisomy 21, and X-linked myotubular myopathy [3]. Molecular work has identified a recurrent missense mutation in ITGA9, encoding an integrin subunit essential for lymphatic vessel development, in fetuses with severe chylothorax poorly responsive to fetal therapy — paralleling the fatal chylothorax phenotype of Itga9-knockout mice and supporting a primary lymphangiogenic defect in at least a subset of cases [14]. Antenatally, pleural fluid accumulation compresses the developing lung, producing pulmonary hypoplasia, and the associated protein and lymphocyte loss can precipitate hydrops fetalis [3]. Postnatally, ongoing chylous loss depletes circulating lymphocytes and immunoglobulins, producing a state of secondary immunodeficiency with a markedly increased risk of nosocomial infection that correlates with the duration of lymphatic drainage [15].

Clinical Presentation

Presentation ranges from antenatally detected pleural effusion with or without hydrops to acute neonatal respiratory distress, occasionally severe enough to require resuscitation at birth [10,16]. Across the 11 individually verified case reports and series reviewed here (Table 1), gestational age at birth ranged from late-preterm to term, though several of the more severe or refractory reports occurred in infants born between 33 and 34 weeks [17,16,10]. Effusions were bilateral in the largest reported series (71.4% of 14 cases) [11] and in one severely affected case with antenatal hydrops [17], while several individual case reports described unilateral, idiopathic disease [18,16,19]. Where reported, male infants predominated (11 of 14 in the largest series) [11], consistent with the male excess described in broader epidemiologic series [12]. Associated antenatal findings included polyhydramnios, ascites, and dysmorphic features prompting chromosomal work-up, which was usually normal in the idiopathic cases reviewed here but abnormal in a minority [16,11]. Several reports describe a biphasic course in which effusion, once thought controlled, recurs after enteral feeding is reintroduced, reflecting the fact that chyle flow — and therefore the biochemical signature of the fluid — depends on dietary long-chain fat intake; this pattern was explicit in one case in which serial taps evolved from a transudate on day 1 of life to a frankly chylous profile only after feeds began [17].

Table 1: Published cases/series of neonatal congenital chylothorax managed with octreotide reviewed here [6,7,24,18,20,21,17,11,19,16,10]; N = 11 reports (2 series, 9 individual cases).

Report	Gestational age	Sex	Laterality	Octreotide regimen	Outcome
Young 2004	Not stated	Not stated	Severe, not stated	40-70 mcg/kg/day SC, 16 days	Survived
Rasiah 2004	Not stated	Not stated	Not stated	0.5-10 mcg/kg/h IV, 10 days	Survived
Sousa 2010	Not stated	Not stated	Idiopathic	Not stated	Survived
Foo 2011	Late preterm	Male	Unilateral, idiopathic	Not stated	Survived
Shah 2012, n=6	Not stated	Not stated	Idiopathic	Not stated	5/6 resolved (83%)
Afsharpaiman 2015	Not stated	Not stated	Not stated	1 mcg/kg/day SC (low-dose)	Survived
Sahoo 2018	33+6 weeks	Female	Bilateral tendency, hydrops	1 mcg/kg/h IV then 10-30 mcg/kg/day SC, 6 weeks	Survived
Yin 2017, n=14	Median 34.7 weeks	11M, 3F	10 bilateral, 4 unilateral	Somatostatin 3.5-7 or octreotide 1-6 mcg/kg/h IV, median 6 days	12/14 survived (85.7%)
Dehghan 2019	Term (39 weeks)	Male	Unilateral	Not stated	Survived
Kobeisy 2020	33 weeks	Female	Right-sided, unilateral	1 mcg/kg/h IV, continuous	Survived
Seo 2021	34 weeks	Male	Bilateral, idiopathic	1 up to 20 mcg/kg/h IV	Survived

Case Table

Table 1 (accompanying floats) summarizes gestational age, sex where reported, laterality, octreotide regimen, and outcome for the 11 individually verified reports. Reported outcomes were favorable in the great majority: resolution was documented in 9 of 11 reports/series, including full resolution in the two largest series (Yin 2017: 12 of 14 survivors, no recurrence; Shah 2012: 5 of 6 resolved) [11,20]. No death directly attributed to octreotide itself was described in any of the 11 reports; the two deaths in the largest series occurred within 48 hours of birth, before octreotide could plausibly have exerted an effect, and were attributed to the severity of the underlying effusion rather than to treatment failure [11].

Diagnostic Approach

Diagnosis begins with pleural fluid sampling once effusion is identified by prenatal ultrasound or postnatal chest radiography/ultrasound. The diagnostic criteria first codified by Buttiker et al. and reproduced across the subsequent literature require a pleural fluid triglyceride concentration ≥110 mg/dL, a total nucleated cell count >1,000 cells/μL with more than 80% lymphocytes, and, where ambiguous, a pleural-fluid-to-serum cholesterol ratio below 1.0 with demonstrable chylomicrons [2,1]. Before enteral feeding is established, however, chyle can appear serous rather than milky and triglyceride content may be low, so an initially "negative" tap does not exclude chylothorax and repeat sampling after feeding is often required, as illustrated in one case series in which pleural fluid analysis converted from a transudate pattern on day 1 to unambiguous chyle by day 13 [17]. A comprehensive antenatal and postnatal work-up — karyotype/microarray, TORCH and viral studies, echocardiography, and, in refractory or atypical cases, lymphoscintigraphy to localize lymphatic leakage — is recommended to exclude structural, infectious, and genetic causes and to identify rare cases amenable to targeted intervention [17,10,3].

Table 2: Pleural fluid and clinical diagnostic criteria for neonatal congenital chylothorax used across the reviewed literature [2,1,17,3].

Parameter	Diagnostic threshold	Notes	Source
Pleural fluid triglyceride	≥110 mg/dL	May be low before enteral feeding begins	buttiker1999
Total nucleated cell count	>1000 cells/μL	With >80% lymphocytes	tutor2014
Pleural fluid/serum cholesterol ratio	<1.0	Used when triglyceride result equivocal	buttiker1999
Chylomicrons	Present	Confirmatory when available	tutor2014

Parameter	Diagnostic threshold	Notes	Source
Ancillary work-up	Karyotype/microarray, TORCH, echocardiography, lymphoscintigraphy if refractory	Excludes syndromic/structural causes	sahoo2018; krishnamurthy2017

Management

Initial management is conservative: pleural drainage, cessation of enteral long-chain-triglyceride feeds with total parenteral nutrition or transition to MCT-enriched formula (which bypasses intestinal lymphatics via direct portal absorption), and correction of protein and electrolyte losses [3,5]. Octreotide, a long-acting somatostatin analogue, is reserved for cases refractory to these measures. It is thought to act by reducing splanchnic and thoracic-duct lymphatic blood flow and by inhibiting several gastrointestinal secretagogues, thereby lowering chyle production and flow [17,16]. Across the case reports and series reviewed, dosing has varied widely: intravenous regimens beginning near 0.5-1 mcg/kg/h and escalated as high as 20 mcg/kg/h [7,10], and subcutaneous regimens from roughly 10 to 70 mcg/kg/day [6,17,21]; duration has ranged from days to as long as six weeks in one refractory case [17]. A 2006 systematic review of 35 children (10 somatostatin, 25 octreotide) reported a positive treatment effect in the majority, with typical intravenous octreotide doses around a median of 68 mcg/kg/day [22], while the 2010 Cochrane review, limited to 19 case reports of 20 neonates given the absence of any randomized trial, found resolution in 70% [23]. A larger 2018 systematic review of 88 octreotide-treated newborns similarly found no consensus dosing protocol, with effectiveness reported in roughly half of cases [8]. Individual case series corroborate a generally favorable, though inconsistent, response: a Chinese single-center series of 14 neonates treated with somatostatin or octreotide showed a significant reduction in daily pleural drainage after treatment initiation (P=.002) and 85.7% survival to discharge without recurrence, obviating pleurodesis or surgery in all survivors [11], and a Sydney series of six idiopathic cases reported resolution in five (83%) [20]. Earlier individual case reports of idiopathic congenital chylothorax responding to octreotide, including one of the first published in a European journal, established the plausibility of this approach before the larger series appeared [24]. By contrast, a Dutch series of seven neonates found no clear, consistent octreotide effect [25], illustrating the heterogeneity of the underlying evidence. Reported adverse effects across this literature include transient hyperglycemia, abdominal distension, transient hypothyroidism, and, less commonly, necrotizing enterocolitis [22,17]. For truly refractory cases, chemical pleurodesis (OK-432, povidone-iodine) and, ultimately, thoracic duct ligation or pleuroperitoneal shunting are described; a large single-center cohort of 178 neonates found that chest-tube output and absolute lymphocyte count, rather than octreotide use per se, best predicted the need for surgical escalation, and proposed a stepwise, objective-criteria-based management algorithm [5].

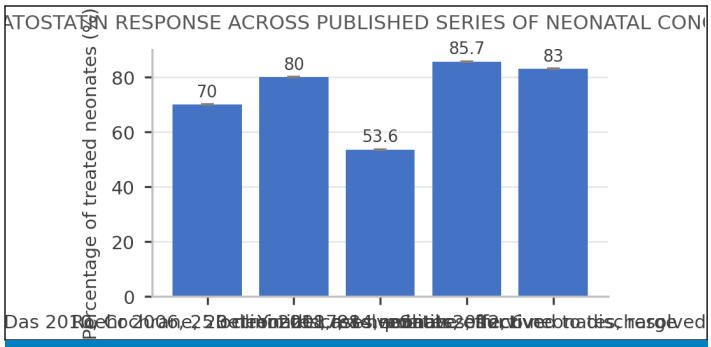

Figure 2: Reported response rates to octreotide/somatostatin across published reviews and series of neonatal congenital chylothorax: 70% resolution in the Cochrane review of 20 neonates [23]; positive effect in 80% of 25 octreotide cases in a 2006 systematic review [22]; 53.6% effective in an 88-neonate systematic review [8]; 85.7% survival to discharge in a 14-neonate series [11]; and 83% resolution in a 6-neonate series [20].

Outcomes/Prognosis

Outcomes depend heavily on gestational age, the presence of hydrops or pulmonary hypoplasia, and

associated chromosomal or structural anomalies rather than on octreotide use alone [13,12]. In the largest pooled analysis, overall mortality was 28% [12], broadly consistent with historical series reporting mortality between 20% and 60% and dependent chiefly on maturity and effusion severity [26]. Among infants who survive to discharge, long-term follow-up (to 12 years in one Austrian cohort) has generally shown no recurrence of pleural effusion, with good neurodevelopmental outcomes in the absence of associated anomalies, though a minority develop later respiratory sequelae such as asthma or residual interstitial change [27]. Prolonged chylous drainage itself carries risk: lymphocyte and immunoglobulin loss produces a secondary immunodeficiency state associated with a roughly threefold increase in nosocomial infection, correlating with the duration of drainage — an additional argument for therapies, including octreotide, that may shorten the course of chylous leakage [15].

Conclusion

The published literature on octreotide for neonatal congenital chylothorax remains limited to case reports, small case series, and two systematic reviews without a completed randomized controlled trial. Within that limitation, the weight of published experience — including a 14-patient series with 85.7% survival and objectively reduced drainage — supports octreotide as a reasonable second-line adjunct to conservative drainage and MCT-based nutrition in cases refractory to initial management, while acknowledging inconsistent responses in at least one published series and the absence of standardized dosing or duration. Diagnosis should follow established pleural-fluid criteria with repeat sampling after feeding is established, and refractory cases should be escalated using objective criteria such as chest-tube output and lymphocyte count toward pleurodesis or surgery. Larger, prospective, ideally multicenter studies are needed to define optimal octreotide dosing and to identify which neonates are most likely to benefit.

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