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ORIGINAL ARTICLE

Cohort study of congenital complete heart block among preterm neonates: a single-center experience over a 15-year period

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Abstract

Congenital complete heart block (CCHB) is a very rare condition, with high risk of mortality. Prematurity is associated with immaturity of the cardiovascular system. Morbidity related to CCHB and prematurity has never been described. We describe a tertiary perinatal center experience over a 15-year period on CCHB management and complications in preterm infants. This is a single-center observational cohort study. All neonates admitted to neonatal intensive care unit with a diagnosis of isolated CCHB between January 2006 and January 2021 were identified. All preterm neonates (< 37 weeks) were compared with a control cohort of term neonates (≥ 37 weeks). Antenatal data, complications of prematurity, medical, and surgical management of CCHB were recorded. Twenty-four neonates with isolated CCHB (16 preterm and 8 term) were born during the study period, including 5 very preterm (< 32 weeks) and 11 preterm (32 to 37 weeks). All very preterm were born via emergency caesarian section without antenatal steroid administration. They had multiple severe morbidities including chronic lung disease, necrotizing enterocolitis, grades 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, and longer periods of mechanical and non-invasive ventilatory support than preterm. Thirteen out of sixteen preterm infants had permanent pacemakers inserted, compared to 1/8 for term newborns. All babies born before 35-week gestation were either paced or died.

Conclusion: Premature neonates with CCHB have high risk of mortality and morbidity especially if undiagnosed and born by unnecessary emergency caesarian section without antenatal steroids. Prematurity below 35 weeks may be associated with death or pacemaker insertion. This supports better antenatal screening to avoid induced prematurity.

What is Known:
- *Congenital complete heart block is a very rare condition associated with high morbidity and mortality.*
- *Antenatal risk factors for poor outcome include fetal hydrops, low ventricular rate (HR <55 beats per minute), and congenital heart defect.*

What is New:
- *Infants born <32 weeks with CCHB had no antenatal steroid administration, and sustained high burden of morbidity (chronic lung disease, intraventricular hemorrhage, and cystic periventricular leukomalacia).*
- *Birth <35 weeks is strongly associated with requiring pacing prior to discharge or death.*

Keywords Congenital heart block · Complete heart block · Prematurity · Neonate

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Abbreviations

CCHB	Congenital complete heart block
CGA	Corrected gestational age
CLD	Chronic lung disease
C-section	Caesarian section
DCM	Dilated cardiomyopathy
ELCH	Evelina London Children's Hospital
HR	Heart rate
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PDA	Patent ductus arteriosus
PPM	Permanent pacemaker
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity

Introduction

Congenital complete heart block (CCHB) is estimated to affect 1:20,000 live births, and is defined as atrioventricular block occurring in utero or within the first month of life [1, 2]. Isolated CCHB is commonly caused by transplacental passage of maternal anti-Ro/SSA and/or anti-La/SSB antibodies during pregnancy, as observed in 95% of mothers of fetus or newborns with CCHB. Pathophysiology involves local inflammation, calcification, and fibrosis of the cardiac conduction system [2, 3]. Although these antibodies appear to be necessary in the pathogenesis of CCHB, they are not sufficient as prevalence of CCHB in newborns from antibody-positive mothers is only 3% [2, 4–6]. CCHB is also associated with congenital heart disease (CHD) in 14–42% of cases, such as left atrial isomerism [4, 7, 8].

Despite advances in antenatal and neonatal care, early morbidity and mortality of CCHB are high. Seventy percent of CCHB-related deaths occur in utero [9]. For liveborn infants with CCHB, 1-year mortality (12–34%) was mostly within the neonatal period [2, 5, 7, 9–12]. Risk factors for poor outcome include fetal hydrops, low ventricular rate (heart rate (HR) < 55 beats per minute (bpm) at presentation or one which drops < 50 bpm), and associated CHD [7, 9, 11–15]. Prematurity is a risk factor for death, though data on neonatal morbidity due to CCHB are scarce [2, 16].

Few data are available for postnatal management of preterm neonates with isolated CCHB. Low systemic blood flow in the first days of life in preterm neonates increases complications of prematurity such as necrotizing enterocolitis (NEC), chronic lung disease (CLD), grades 3–4 intraventricular hemorrhage (IVH), and periventricular leukomalacia (PVL) [17, 18]. Preterm neonates with CCHB may have a reduced cardiac output from low heart rate, and a left-to-right shunt through the patent ductus arteriosus (PDA), decreasing systemic blood flow, with limited compensatory capacity. Management of CCHB in preterm infants can be challenging and often requires early temporary or permanent pacemaker placement, as reported in 46% of liveborn infants with CCHB [7].

We describe the experience of our tertiary perinatal and cardiothoracic center, in the management and outcomes of isolated CCHB with a particular focus on very preterm infants, in a cohort of infants born over a 15-year period.

Methods

This retrospective observational cohort study was conducted at the Evelina London Children's Hospital Neonatal Unit (ELCH), London (UK), a tertiary neonatal center with onsite pediatric cardiology and cardiothoracic surgery. All preterm neonates born at less than 37-week gestation admitted to neonatal intensive care unit (NICU) with a diagnosis of isolated CCHB between January 2006 and January 2021 were identified. Their outcomes were compared with a control cohort of term neonates born after 37 weeks with a diagnosis of isolated CCHB and admitted to NICU during the same period. Neonates with congenital cardiac malformations were excluded from the analysis.

As the data analysis was retrospective and no additional data were collected beyond those required for standard medical care, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was not required. A clinical audit was registered with the Guy's and St Thomas' NHS Foundation Trust Audit Committee (number 8907). Because retrospective data were collected from chart reviews only, consent from patients and parents or guardians was not obtained.

Demographic, clinical, and laboratory data were collected from electronic patient records (Astraia, BadgerNet®, Electronic Patient Records, Patient Archiving and Communication System).

Antenatal data collected included maternal age and gestation at CCHB diagnosis, maternal antibody status (anti-Ro/SSA, anti-La/SSB), presence or absence of known autoimmune disease, associated fetal anomalies, initial ventricular rate at diagnosis, and antenatal treatment for CCHB. Perinatal and postnatal data obtained were gestation at birth, birth weight, sex, delivery method, ventricular rate at birth, and dilated cardiomyopathy (DCM) (defined as left ventricular dilatation [diastolic ventricular diameter z-score greater than + 2] and fraction shortening < 28%). Interventions including inotrope requirement, need for surgical or trans-catheter PDA closure and pacemaker placement, were recorded.

Outcomes and complications associated with prematurity were identified: duration of invasive and non-invasive respiratory support, CLD, early (< 72 h) and late (> 72 h) neonatal sepsis, NEC Bell stage ≥ 2, abdominal surgery for NEC or spontaneous intestinal perforation, retinopathy of prematurity (ROP) stage ≥ 3, cystic PVL, severe IVH (grades 3 and 4). Clinical signs suggestive of neonatal lupus and patient outcomes and survival to home discharge were recorded.

Statistical methods

Statistical analyses were performed with IBM SPSS statistics 25.0 (SPSS Inc., Chicago, IL, USA). Due to small numbers, continuous variables were reported as median (interquartile range) and frequencies. Continuous variables (maternal age [years], HR [beats per minute], gestation at antenatal diagnosis [weeks], length of respiratory support [days]) were compared with non-parametric tests (Kruskal–Wallis or Mann–Whitney U test). Statistical significance was assumed at $p < 0.05$.

Results

Over the study period, 29 neonates were admitted to NICU with a diagnosis of CCHB. Five had associated congenital heart malformations and were excluded from the analysis. Of the 24 neonates with isolated CCHB, 16 were born preterm, and 8 were born at term. Data were analyzed by gestation groups: very preterm (< 32 weeks, $n = 5$), preterm (≥ 32 weeks and < 37 weeks, $n = 11$), and term neonates ($n = 8$). Antenatal and perinatal findings are summarized in Table 1. All five very preterm neonates were outborn, whereas 10/11 preterm neonates were inborn. All very preterm neonates were born via emergency caesarian section (C-section), with no mother having received antenatal steroids for fetal maturation. All eleven preterm neonates were born via C-section: 5 following planned elective C-section, of whom 1 had antenatal steroids for fetal maturation. Of the 6 born via emergency C-section, 2 (17%) received antenatal steroids. Fetal bradycardia was the main reason for emergency C-Section (4/5 very preterm and 4/6 preterm); these neonates were postnatally diagnosed with CCHB. Other reasons were worsening CCHB and maternal reasons (i.e., severe pre-eclampsia, cholestasis of pregnancy). Term neonates were born either by elective C-Section (7/8) or by vaginal delivery (1/8); all were antenatally diagnosed with CCHB.

Table 2 summarizes neonatal morbidity among the 3 gestation groups. All very preterm, 9/11 preterm neonates and none of the term neonates required inotropic support to maintain optimal cardiac output. Seventy-one percent (10/14) of these infants required multiple inotropic agents. Six of these babies who required three or more inotropic agents required temporary pacing or permanent pacemaker insertion during their inpatient stay. Among the 14 patients who required inotropic support, 12 received isoprenaline as first agent for its combined chronotropic and inotropic effect, with dopamine (9/14), milrinone (3/14), adrenaline (2/14), and dobutamine (2/14) introduced as second-line treatments. One patient was treated with salbutamol.

Three very preterm patients required PDA closure, either by surgical ligation (2/3) or by trans-catheter closure (1/3), as systemic blood flow was significantly reduced by left-to-right shunt through the PDA. Temporary cardiac pacing was performed in 5 patients (3/5 very preterm, and 2/11 preterm), at a median age of 45 days for very preterm (range 3–63 days of age) and 2.5 days for preterm (range 2–3 days). Permanent pacemaker (PPM) insertion was performed in all 5 very preterm neonates at term corrected gestational age (CGA) (range 38 + 1 weeks CGA to 8 weeks post-term CGA), with median weight at time of PPM insertion 2700 g (range 2500–4500 g). Permanent pacemakers were inserted via a limited median sternotomy, with a single epicardial ventricular lead and an abdominal generator in all but one. The latter had infection of temporary leads placed via a sternotomy; permanent pacemaker was placed via a left thoracotomy after a period of temporary trans-venous pacing while receiving treatment for infection. Impact of HR and gestation on outcome (pacing and death) are detailed in Fig. 1. All babies born before 35-week gestation ($n = 11$) and 4/13 babies born after 35 weeks were either paced or died, which was statistically significant ($p < 0.0001$ on Fisher exact test, OR 2.43 (1.2–4.9)).

All five very preterm neonates, 9/11 (82%) preterm were intubated in the first 24 h of life, compared to none of the term babies. Among patients with temporary epicardial pacing, 3/5 (all very preterm) developed late onset sepsis (2 patients methicillin sensitive staph aureus, 1 patient coagulase negative staphylococcus), and 3 developed wound infection. NEC with pneumatosis intestinalis was diagnosed in 2 patients; both medically managed. One patient required abdominal surgery for gastric and jejunal perforations. All major comorbidities occurred in the very preterm population, including CLD (Table 2).

Three preterm neonates (19%) died before being discharged home (median corrected gestation age at death 35 + 2 weeks [32 weeks–40 weeks], median postnatal age 5 days [2–44 days]) (Supplement, Table 3). No term neonates died before discharge, and 1 required PPM insertion before discharge.

Table 1 Baseline antenatal and perinatal findings

	Very preterm neonates < 32 weeks ($n = 5$)	Preterm neonates 32 to 36 + 6 weeks ($n = 11$)	Term population ($n = 8$)	p value (sig < 0.05)
Antenatal findings				
Fetuses with antenatal diagnosis of CCHB	1	10	8	
Median maternal age (years, interquartile range)	33 (33–35)	31 (29–34)	27 (23–28)	0.01
Median gestation at diagnosis (weeks, interquartile range)*	29	22 (22-25)	21 (19–21)	
Antibody status				
Anti-Ro positive and Anti-La positive	2	5	3	
Anti-Ro positive	1	4	3	
Anti-Ro/La negative	1	0	2	
Unknown	1	2	0	
Maternal autoimmune disease	2	6	1	
Systemic lupus erythematosus	1	3	0	
Sjögren's syndrome	1	2	1	
Median initial ventricular rate at antenatal diagnosis (beats per minute, interquartile range)^	-	65 (58–79)	62 (57–65)	
Hydrops fetalis	0	1	0	
Antenatal steroids for fetal maturation	0	3	0	
Antenatal medication for CHB	1	5	2	
Fluorinated steroids (oral)	1	5	2	
Beta sympathomimetics (oral)^^	0	4	0	
Perinatal and birth details				
Median gestation (weeks, interquartile range)	29.7 (28.7–30.3)	34.2 (33–35.2)	38 (37.7–38.4)	< 0.001
Median birth weight (grams, interquartile range)	1410 (1350–1500)	1935 (1798–2461)	2787 (2615–2918)	0.001
Sex (male:female)	1:4	1:1.2	1:7	
Delivery method				
Elective lower segment caesarian section	0	5	7	
Emergency lower segment caesarian section	5	6	0	
Spontaneous vaginal delivery	0	0	1	
Median initial ventricular rate (beats per minute, interquartile range)	56 (55–65)	50 (46–54)	62 (57–65)	0.05

*Details available for 16/19 with antenatal diagnosis of CCHB, including only one very preterm < 32 weeks

^Details available for 10/19 babies with antenatal diagnosis of CCHB

^^All mothers who received beta sympathomimetics in pregnancy following antenatal diagnosis of CCHB also received fluorinated steroids

Discussion

Our work describes the perinatal management, morbidity, and mortality of CCHB in a neonatal cohort over a 15-year period in a tertiary center, particularly highlighting major morbidities experienced by premature neonates < 32-week gestation, as most are born undiagnosed, and emergently without antenatal steroid administration.

In a large single-center evaluation of CCHB, Jaeggi et al. noted worse outcomes when a fetal diagnosis of CCHB had been made [9]. They suggested the fetal group may represent a more severe spectrum of disease. In comparison, the babies born at term in our cohort all had a fetal diagnosis of CCHB and appeared to follow a more stable course, with only 1 requiring pacemaker insertion prior to discharge home. Among our very preterm cohort, however, only 1 had a fetal diagnosis of CCHB, and all required permanent pacemaker insertion prior to discharge. All 5 infants born < 32-week gestation were delivered via emergency C-section for suspected fetal distress without antenatal steroid administration. Among the preterm neonates born < 34 weeks, 3/16 (19%) received antenatal steroids for fetal maturation, which

Table 2 Neonatal morbidity in patients with isolated CCHB across gestation groups

Neonatal morbidity	Very preterm neonates < 32 weeks ($n = 5$) (%)	Preterm neonates 32 to 36+6 weeks ($n = 11$) (%)	Term population ($n = 8$) (%)	p value (sig < 0.05)
Congestive heart failure				
Requiring inotropes	5 (100)	9 (82)	0	
Requiring temporary pacing	3 (60)	3(27)	0	
Permanent pacemaker insertion	5 (100)	8 (73)	1 (13)	
Late onset neonatal sepsis	3 (60)	0	0	
Median duration of respiratory support (days, interquartile range)	62 (60–80)	2 (1–4)	0	< 0.001
Mechanical ventilation (days, interquartile range)	18 (4–63)	1 (1–4)	0	< 0.001
Non-invasive respiratory support (days, interquartile range)	12 (10–58)	1 (0–2)	0	0.001
Necrotizing enterocolitis	2 (40)	0	0	
PDA closure (surgical or endovascular)	3 (60)	0	0	
Chronic lung disease*	4 (80)	0	0	
Grades 3–4 intraventricular hemorrhage	2 (40)	0	0	
Cystic periventricular leukomalacia	1 (20)	0	0	
Non cystic periventricular leukomalacia	2 (40)			
Death before home discharge	0	3	0	

*Oxygen dependency at 36 weeks CGA or 28 days in patients who survived to discharge or transfer

is significantly below UK Neonatal National audit targets of 85% for the 24- to 34-week preterm population. Lack of antenatal steroids and unplanned emergency delivery with CCHB likely exposed them to greater complications of prematurity, with almost all extreme preterms developing severe comorbidities (Table 2). Our preterm population had longer rates of ventilator support compared to our term patients (Supplement, Table 5).

All babies born < 35/40 required pacemaker implantation prior to discharge, or died (Fig. 1). The three patients within our cohort (13%) who died were all between 32- and 35-week gestation at birth, which is higher than reported

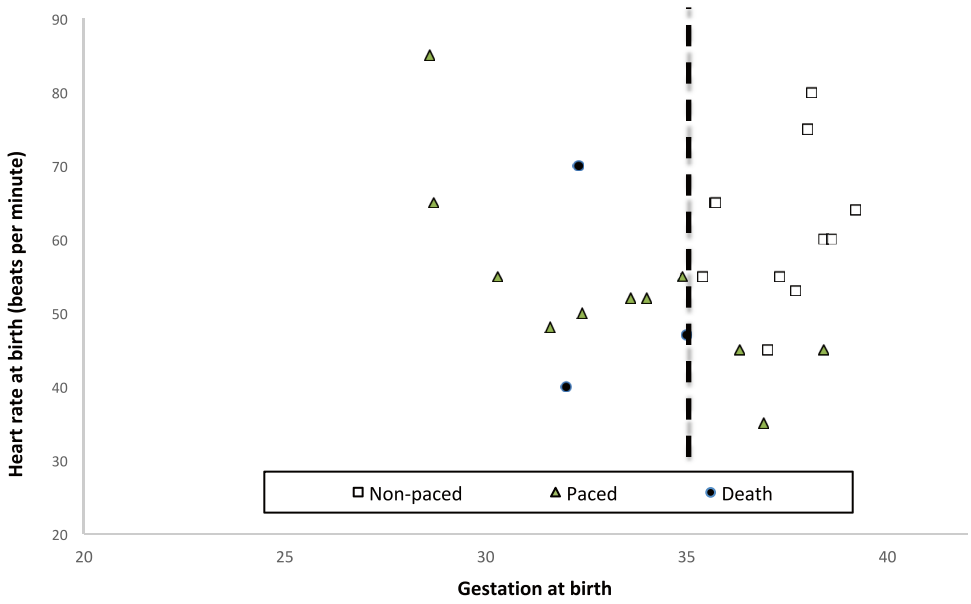

Fig. 1 Heart rate at birth and gestation at birth with respect to outcomes (pacing and death)

by Ho A et al. (8% in the neonatal period), potentially reflecting the high-risk background of our patients (lower gestation at birth [35 weeks versus 37 weeks] and lower heart rate at birth [55 bpm versus 60 bpm]) [12]. Our data confirms previous findings of prematurity as a significant risk factor for worse outcomes [16, 19]. Exposure to anti-Ro and anti-La antibodies can induce an immune reaction within the myocardium, resulting in endocardial fibroelastosis and dilated cardiomyopathy, with or without conduction abnormalities [20, 21]. Endocardial fibroelastosis is associated with mortality > 50%, while mortality with associated dilated cardiomyopathy is 100% [19]. Antenatal exposure to maternal antibodies for these three patients (2/3 anti-Ro positive, 1/3 unknown) may have contributed to immune-mediated myocardial damage, although as 86% of our cohort were anti-Ro/anti-La positive, prematurity was likely the additive factor causing the mortality. Eighty-six percent of tested mothers in our cohort were anti-Ro/anti-La positive. This rate is consistent with reported literature of up to 88% of the mothers of babies born with CCHB being antibody-positive [4, 5, 12, 13, 22].

There is currently no expedient way to distinguish between fetal bradycardia from hypoxic fetal distress or CCHB. Diagnosis of CCHB relies on fetal medicine expertise showing dissociation between atrial and ventricular contractions on M-Mode imaging. CCHB is much rarer than fetal bradycardia from fetal distress, justifying the need to deliver these babies by emergency C-section, without antenatal steroids. Developing a method of discriminating between these two conditions could be an area for further research. Antenatal diagnosis of CCHB allows antenatal interventions (fluorinated steroids) to limit inflammation in the fetal heart, and appropriate perinatal management and planned delivery to optimize outcome [23].

The main objective of the congenital CCHB management is to assess, monitor, and support low cardiac output resulting from bradycardia. In preterms, this goal is even more important given the narrow autoregulation plateau for organ blood flow, increasing susceptibility to severe complications such as severe IVH, and to hypoxia in kidneys and intestines [24–26]. Interestingly, there was no significant difference between antenatal HR and HR at birth between the groups despite differing outcomes (Supplement, Table 4). Also, no patients required surgery for NEC, despite periods of presumed low cardiac output due to low heart rate, though one patient required surgery for intestinal perforation.

In newborns with complete CCHB, any reduction in cardiac output from bradycardia may initially be maintained through increased stroke volume and contractility. However in preterms, inotropy reserve is reduced due to myocardial immaturity [27, 28]. Therefore, initial management aimed to achieve a minimum, critical heart rate threshold and support inotropy to maintain adequate systemic blood flow and end-organ perfusion. HR < 55 bpm has been associated with poor outcomes [9, 11]. We started isoprenaline in all patients with heart rate < 55 bpm, mostly on day 1 (12 patients). Escalation of treatment relied on regular clinical and lactate assessment. Main chronotropic drugs used in our population were dopamine and adrenaline. The second objective of management was to maintain a mean blood pressure within the autoregulation plateau for all organs. A combination of low systemic diastolic blood pressure and longer diastole period can contribute to decreased mean blood pressure and blood flow redistribution (Supplement, Fig. 2) [29]. In challenging situations when adequate organ perfusion could not be maintained, PDA closure was performed in three patients. In sick preterm neonates, trans-catheter closure may improve procedural stability and reduces duration of mechanical ventilation [30].

If medical management failed to maintain HR > 55 bpm and systemic perfusion was inadequate, pacing was considered. Premature neonates present unique technical difficulties for pacemaker implantation, due to their weight, lack of subcutaneous tissue, and future growth. Endocardial lead placement is associated with venous obstruction; therefore, epicardial pacing is preferred. Also, the size of the generators in permanent pacemakers may be prohibitively large and a staged approach may be required, with temporary externalized epicardial pacing, followed by permanent system implantation at a later date [14]. Temporary pacing was associated with infection risk. The majority of surviving preterm patients (85%) had permanent pacemaker insertion close to term corrected gestational age, which is higher than 76% reported by Ho A et al. in a more mature cohort (median gestation at birth 37 weeks) who were all diagnosed prenatally [12].

Our study has several limitations: retrospective data collection, single-center recruitment, and small sample size due to low prevalence of CCHB. This limited interpretation of the results, and did not allow statistical analysis between survivors and non-survivors. Antenatal findings and maternal antibody status were not available for all patients. There was possible referral bias as our neonatal unit was more likely to have unwell preterm neonates with CCHB; clinically stable term babies with CCHB are more likely to have been managed at external hospitals in the immediate postnatal period. Depending on the length of follow-up of published data, 6–18% of CCHB infants develop dilated cardiomyopathy and congestive heart failure, and may die or require cardiac transplantation [11, 16, 21, 31, 32]. In our study, we were only able to capture short-term outcomes.

In conclusion, premature neonates with CCHB have a high risk of mortality and morbidity. Due to the rarity of this condition, prospective long-term data collection is important in understanding morbidity and outcomes for these patients. Early antenatal diagnosis, close fetal surveillance, antenatal

corticosteroid administration prior to preterm delivery, and planned delivery in an institution with neonatal and cardiac expertise are important in managing these patients. Postnatal cardiovascular management is challenging. Maintaining HR > 55 bpm, supporting myocardial function, and closing the duct are currently the main interventions, before early temporary and later permanent pacing, which both add specific risks. In our study, infants born < 32 weeks with undiagnosed CCHB have a high burden of morbidity due to unplanned delivery without antenatal steroids, and birth < 35 weeks is strongly associated with requiring pacing prior to discharge or death. Rapidly identifying and diagnosing the in utero fetus with CCHB could avoid unnecessary emergency C-section and prevent the burden associated with these high-risk births.

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Authors' contributions HH conceptualized the study, collected data and performed data analysis, drafted the initial manuscript, and revised the manuscript with input from all the co-authors. WR reviewed the data and contributed to revision of the manuscript. HB collected data and contributed to revision of the manuscript. ER reviewed the data and contributed to revision of the manuscript. VMP conceptualized the study, collected data and performed data analysis, and contributed to revision of the manuscript.

Data and materials availability N/A

Code availability N/A

Declarations

Ethics approval As the data analysis was retrospective and no additional data were collected beyond those required for standard medical care, a full ethics review under the terms of the Governance Arrangements of Research Ethics Committees in the UK was not required. A clinical audit was registered with the Guy's and St Thomas' NHS Foundation Trust Audit Committee (number 8907). Because retrospective data were collected from chart reviews only, consent from patients and parents or guardians was not obtained.

Consent to participate N/A

Consent for publication All authors have approved the final submitted version for publication and agree to be accountable for all aspects of the work.

Conflict of interest The authors declare no competing interests.

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