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Original Article

Factors influencing bacteraemia in patients with isomerism and CHD: the effects of functional splenic status and antibiotic prophylaxis

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Abstract *Background:* "Heterotaxy syndrome", best segregated as isomerism, is characterised by laterality defects of the thoraco-abdominal organs, causing functional impairment. In particular, the spleen is frequently affected, increasing susceptibility to bacteraemia. This study explored factors that may increase the risk of bacteraemia in patients with isomerism. *Methods:* We identified patients with CHD and isomerism. Review of outpatient, inpatient, and surgical records was conducted to collect data and determine trends in the cohort. A Cox regression analysis was conducted to determine factors influencing freedom from bacteraemia (Fig 1). *Results:* We identified 83 patients with CHD and isomerism – 17 (20%) who had documented episodes of bacteraemia with a total of 21 episodes. A majority (86%) were nosocomial. The median age at the time of bacteraemia was 4 months. Although splenic anatomy did appear to influence the risk of bacteraemia in univariate analysis, this significance was lost with multivariate analysis. None of the other factors was significantly associated in either univariate or multivariate analysis. *Conclusion:* Specific factors such as splenic anatomy, atrial appendage isomerism, and antibiotic prophylaxis status are not significantly associated with the risk of bacteraemia in patients with CHD and isomerism. Nosocomial infections represent a majority of bacteraemia in these patients.

Keywords: Isomerism; heterotaxy; bacteraemia; antibiotics; asplenia; polysplenia

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So-called "heterotaxy syndrome" is characterised by isomerism of the thoracic organs and random arrangement of the abdominal organs.[1] Although once distinguished on the basis of splenic anatomy, segregation on the basis of the morphology of the atrial appendages is now considered optimal.[2] Those with right isomerism will have atrial appendages that are broad and pyramidal. Such patients typically have complex congenital malformations of the heart requiring univentricular palliation, tracheobronchial angle of >135°, bilaterally trilobed lungs, intestinal malrotation, and absence of the spleen.[2–6] Those with left isomerism will have atrial appendages that are both narrow and finger like, less complex congenital malformations of the heart, symmetrical tracheobronchial angles of <135°, bilaterally bilobed lungs, and multiple spleens.[4,7,8]

These findings are more than anatomic curiosities and frequently have significant consequences – for instance, those with isomerism can have functional asplenia in the setting of a normally located solitary spleen or multiple spleens.[9] In addition, functional asplenia may also leave these patients at increased risk for thrombocytosis and subsequent thromboembolic events.[10–12] Postoperative outcomes and complications in these children have also been demonstrated to be different.[13–15] It has long been recognised that

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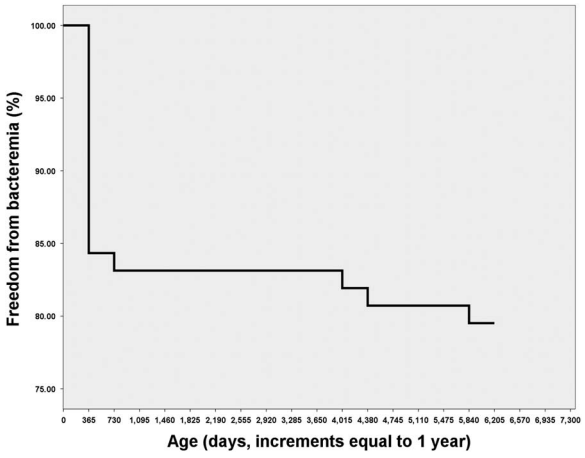

Figure 1.
Kaplan–Meier curve demonstrating freedom from bacteraemia in patients with isomerism.

those with isomerism are at higher risk for morbidity and mortality.[14,16–19] A part of these increases is related to the presumed increased risk of bacteraemia in this population.[18,20–27] There are limited data, however, regarding bacterial infection in the population of patients with isomerism, and on how this can be effectively prevented and managed. In this study, we aimed to characterise the infectious characteristics of a cohort of patients with isomerism and to determine the impact of splenic anatomy and other factors on their bacteraemic risk in only children with isomerism; we did not compare with children without isomerism.

Methods

Our methodology was approved by the Institutional Review Board at our institution and complies with the Declaration of Helsinki. Medical records of all patients with CHD and isomerism who were cared for at Children's Hospital of Wisconsin since 1998, the year electronic medical records was implemented at the institution, were reviewed. This included both patients born in or after 1998, as well as those born earlier who transitioned their care to our heart centre after 1998. Those who were born before 1998 at our institution and remained alive at the time of establishment of our electronic medical record system were also captured.

The charts were reviewed, and patients were included if they had CHD and isomerism. CHD was defined as any intracardiac lesion or abnormality of systemic venous return to the heart. Isomerism was defined as having the aforementioned CHD in the setting of abnormal arrangement of the abdominal organs, pulmonary isomerism, or anatomic splenic abnormalities. The diagnosis of isomerism for this study was established on the basis of chart review. Bacteraemia was defined as a positive blood culture at our institution. The state of antibiotic prophylaxis against encapsulated bacteria was also assessed for all patients. Compliance of the use of prophylactic antibiotics could not be assessed.

Data regarding cardiac anatomy were obtained primarily from echocardiographic investigations, although cardiac MRI and cardiac catheterisation data were also available for some patients. Anatomic splenic status in all but two patients was based on abdominal ultrasonography. Patients were excluded if they did not have CHD, isomerism, or ample clinical data. Children with chromosomal anomalies were not excluded from this study.

The intracardiac features considered to indicate the presence of isomeric right as opposed to left atrial appendages were assessed independently by two authors (R.L. and R.H.A.), with cognisance taken also of the findings in the other systems of organs. These included, but were not limited to, overall cardiac anatomy, venoatrial connections, and splenic anatomy.

Infectious disease end points for which data were collected included, but were not limited to, splenic morphology, prophylactic state, history of bacteraemia, as well as organisms cultured during episodes of bacteraemia. Categorical variables are presented as absolute numbers and percentages, whereas continuous variables are presented as medians and ranges. Continuous variables were compared using a Mann–Whitney U–test, and categorical variables were compared using χ^2 analysis.

Survival analysis was carried out using Cox regression to assess the impact of selected variables of interest in predicting episodes of bacteraemia. Data analysis were conducted using SPSS (Chicago, Illinois, United States of America). A p-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics

A total of 83 patients were identified as having CHD and isomerism. Of the group, 37% were known to have absence of the spleen, 57% had anatomic polysplenia, and 6% had a normally located spleen. Episodes of bacteraemia occurred in 17 patients (20%). Patients with and without episodes of bacteraemia did not differ in their baseline characteristics other than with respect to splenic anatomy. Perhaps surprisingly, those with a history of bacteraemia were more likely to have multiple spleens, whereas those without a history of bacteraemia were more likely to

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Table 1. Characteristics of patients with and without a history of bacteraemia.

	Patients with bacteraemia (n = 17)	Patients without bacteraemia (n = 66)	Univariate p-value	Multivariate p-value
Age at bacteraemia	2.47 ± 1.88	–	–	–
Primary cardiac lesion				
Aortic stenosis	0 (0)	1 (2)	0.831	0.961
Atrial septal defect	0 (0)	2 (3)		
Coarctation of the aorta	0 (0)	1 (2)		
Complete atrioventricular septal defect	10 (59)	40 (59)		
Incomplete atrioventricular septal defect	0 (0)	1 (2)		
Doublet-inlet left ventricle	0 (0)	3 (3)		
Double-outlet right ventricle	3 (18)	7 (11)		
Hypoplastic left heart syndrome	3 (18)	4 (6)		
Interrupted aortic arch	1 (5)	1 (2)		
L-transposition of the great arteries	0 (0)	1 (2)		
Pulmonary stenosis	0 (0)	1 (2)		
Tetralogy of Fallot	0 (0)	1 (2)		
Ventricular septal defect	0 (0)	3 (4)		
Cardiac repair status				
Univentricular	11 (65)	46 (70)	0.829	0.864
Biventricular	5 (29)	18 (27)		
Transplant	2 (6)	2 (3)		
Splenic anatomy				
Normally located, solitary spleen	0 (0)	10 (15)	0.032	0.124
Multiple spleens	8 (47)	13 (20)		
Absence of the spleen	9 (53)	43 (65)		
Antibiotic prophylaxis prescribed	13 (77)	45 (68)	0.507	0.745
Atrial appendage isomerism				
Right	9 (53)	44 (67)	0.294	0.739
Left	8 (47)	22 (33)		
Abdominal situs				
Left-sided stomach with right-sided liver	9 (53)	20 (30)	0.097	0.744
Right-sided stomach with left-sided liver	4 (24)	27 (41)		
Left-sided stomach with midline liver	4 (23)	19 (29)		

have absence of the spleen or a normally located and solitary spleen (Table 1). Total follow-up time for the cohort was 587 patient years, with a mean follow-up time of 7.0 years/patient.

Bacteraemia overview

The nature of the episodes of bacteraemia is provided in Table 2. There was a total of 21 instances of bacteraemia, with a total of 22 cultured bacterial organisms. The median age at bacteraemia was 4 months, with a range from 15 days to 19 years. The most common bacterial organisms were coagulase-negative *Staphylococcus*, *Streptococcus viridans*, and *Escherichia coli*, where each grew in three (14%) cultures. *Enterococcus*, *Staphylococcus aureus*, *Streptococcus*, and *pneumoniae* each grew in two (9%) cultures. Group B *Streptococcus*, *Citrobacter*, *Enterobacter*, *Stenotrophamonas maltophilia*, *Klebsiella oxytoca*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* each grew in one (5%) culture (Table 2). Using susceptibility data from our institution, eight of 22 (36%) cultured organisms should have been susceptible to amoxicillin, three of 22 (14%) should have had intermediate susceptibility to amoxicillin, and 11 of 22 (50%) should have been resistant to amoxicillin.

Cardiac anatomy in those with bacteraemia

Of the 17 patients with bacteraemia, 10 (59%) had a primary cardiac diagnosis of atrioventricular septal defect with common atrioventricular valve, three (18%) had double-outlet right ventricle, three (18%) had hypoplastic left heart syndrome, and one (5%) had isolated interruption of the inferior caval vein. The diagnosis of isomerism was made prenatally in 11 (65%) patients, with postnatal diagnosis made at a mean age of 5 days in the remainder. Left isomerism was found in eight (47%) patients and right isomerism in nine (53%). Abdominal arrangement was usual in five patients (29%), mirror imaged in four (24%), mixed in four (24%), and considered indeterminate in four (24%). The circulation was functionally univentricular in 11

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Table 2. Patient-level data of patients with history of bacteraemia.

Patients	Anatomic splenic status	Functional splenic status	Prophylaxis at time of SBI	SBI episode	Age at SBI episode (months)	Organisms	Hospital acquired	Death from SBI episode
1	Polysplenia	–	Yes (amoxicillin)	1	1	*Staphylococcus aureus*	Yes	No
2	Asplenia	Asplenia	Yes (amoxicillin)	1	3	CONS	Yes	No
3	Asplenia	Asplenia	Yes (amoxicillin)	1	3	*Staphylococcus aureus*	Yes	No
				2	4	*Enterococcus*	Yes	No
4	Polysplenia	Normal	No	1	1	Group B *Streptococcus*	No	No
5	Asplenia	Asplenia	Yes (amoxicillin)	1	2	*Citrobacter*, *Enterobacter*	Yes	No
6	Asplenia	Asplenia	No	1	1	*Stenotrophamonas maltophilia*	Yes	No
7	Asplenia	Asplenia	Yes (amoxicillin)	1	0.5	*Klebsiella oxytoca*	Yes	No
				2	34	*Streptococcus pneumoniae*	Yes	Yes
8	Polyspenia	–	Yes (amoxicillin)	1	7	*Pseudomonas aeruginosa*	Yes	Yes
9	Polysplenia	–	No	1	0.5	*Klebsiella pneumoniae*	Yes	No
				2	3	*Enterococcus*	Yes	No
10	Polysplenia	–	No	1	18	CONS	Yes	No
11	Asplenia	Asplenia	Yes (amoxicillin)	1	4	*Streptococcus pneumoniae*	Yes	No
12	Asplenia	Asplenia	Yes (amoxicillin)	1	135	*Streptococcus viridans*	Yes	No
13	Polysplenia	–	Yes (amoxicillin)	1	5	*Escherichia coli*	Yes	No
14	Polysplenia	–	No	1	7	*Streptococcus viridans*	Yes	No
				2	76	*Escherichia coli*	No	No
15	Polysplenia	–	No	1	191	*Streptococcus viridans*	No	No
16	Asplenia	Asplenia	Yes (amoxicillin)	1	2	*Escherichia coli*	Yes	No
17	Asplenia	Asplenia	Yes (amoxicillin)	1	122	CONS	Yes	No

CONS = coagulase negative staphylococcus; SBI = severe bacterial infection

(65%) patients, biventricular in five (29%), and transplant in one (6%).

Antibiotic prophylaxis

Out of the total cohort, 58 (70%) patients were prescribed prophylactic antibiotics as a component of care. Such prophylaxis consisted of either ampicillin or amoxicillin in all patients. Compliance with prophylaxis could not be accurately assessed. Bacteraemia occurred in a total of six (24%) of those not receiving prophylactic antibiotics and in 11 (19%) of the patients prescribed prophylactic antibiotics. It was not possible independently to confirm compliance with the prophylactic regime.

The median age at commencement of antibiotic prophylaxis was 8 days, with a range from zero to 850 days. Of those who were prescribed prophylactic antibiotics, the regime was discontinued in six patients at a median age of 16 years, with a range from 0.5 to 23 years. Of those with discontinued prophylaxis, four (66%) had anatomic asplenia, one (17%) had anatomic polysplenia, and one (17%) had a normally located spleen.

Almost two-thirds (65%) of our patients were knowingly on prophylaxis at the time of bacteraemia, with the remaining one-third (35%) not receiving prophylactic antibiotics at the time of bacteraemia. Of these six patients, five had anatomic polysplenia, whereas the remaining patient had anatomic asplenia.

Nosocomial versus community-acquired bacteraemia

Nosocomial infections accounted for 18 (86%) instances of bacteraemia; 19 instances of nosocomial bacteriaemia occurred over a total of 16 patients. The majority of these infections occurred postoperatively, with lines in place. Of the episodes with nosocomial source of bacteraemia, patients were on prophylactic antibiotics at the time of 14 of 18 (78%) of these episodes. Of the bacteria isolated from nosocomial instances of bacteraemia, six of 18 (33%) should have been susceptible to amoxicillin.

Community-acquired infections accounted for three (14%) of the instances of bacteraemia. The three instances of community-acquired bacteraemia occurred over a total of three patients, all of whom were not on prophylaxis and all of whom had multiple spleens. These patients had growth of Group B *Streptococcus*, *Streptococcus viridans*, and *Escherichia coli* from their blood cultures. According to the susceptibilities at our institution, the former two bacteria are generally susceptible to amoxicillin, whereas the latter is not susceptible.

Children greater than 5 years of age

With regard to older children, there were only four instances of bacteraemia that occurred after 5 years of age. These patients ranged from 6 to 15 years of age. Of these episodes, two (50%) were due to *Streptococcus virdans*, with the others due to *Escherichia coli* and coagulase-negative *Staphylococcus*. At the time of bacteraemia, two of the patients with multiple spleens were not receiving prophylactic antibiotics, whereas the other two patients, known to have asplenia, were receiving prophylaxis. Both patients with multiple spleens had community-acquired bacteraemia, whereas both with asplenia had nosocomial bacteraemia. None of these patients with bacteraemia died. Of the three organisms identified, one should have been susceptible to amoxicillin according to the known susceptibilities at our institution.

Mortality

Bacteraemia resulted in the death of two patients. These two patients accounted for 12% of all patients in this cohort who had an episode of bacteraemia, and 2% of the overall group. Among them, one patient (patient 7, Table 2) was 34 months of age at the time of death and was experiencing his second episode of bacteraemia. His first episode occurred at less than one month of age, due *Klebsiella oxytoca* infection, whereas the second episode was due to *Streptococcus pneumoniae*. The first episode was nosocomial, whereas the second episode was believed to be community acquired. The child had an atrioventricular septal defect with common atrioventricular valve, double-outlet right ventricle, pulmonary atresia, left-sided and anterior aorta, and a right-sided aortic arch. He had bronchi that were bilaterally right in morphology. He had undergone a Blalock–Taussig shunt, as well as a bidirectional Glenn anastomosis. In the time leading to his death, the child had presented to the emergency room after he had a seizure in the setting of a fever and large emesis where he was found to be hypoxic. He was transferred to the cardiac ICU where he required extracorporeal membrane oxygenation and high-dose inotropic support. A few hours into his hospitalisation, blood cultures showed growth of *Streptococcus pneumoniae*. The child was already on broad-spectrum antibiotics. The child became anuric, coagulopathic, and continued to have haemodynamic compromise. After discussion with his family, support was withdrawn on the day of admission. This child did have anatomic asplenia and was receiving prophylactic antibiotics.

The second death (patient 7, Table 2) was of a baby girl aged 7 months with an atrioventricular septal defect, tetralogy of Fallot, bilateral superior caval veins with the left vein draining to a coronary sinus,

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interruption of the inferior caval vein, and a right aortic arch. She had been admitted to our unit for atrioventricular septation and placement of a conduit from the right ventricle to the pulmonary arteries. She had been noted previously to have multiple spleens by abdominal ultrasound and had been commenced on prophylactic antibiotics early on during hospitalisation. Postoperatively, she required extracorporeal membrane oxygenation support for reduced ventricular function, from which she was weaned after a period of 12 days. Following decannulation, she required escalation in her inotropic support and re-opening of her sternum. At that time, *Pseudomonas aeruginosa* was cultured from her blood. She was placed on appropriate antibiotic therapy. She was also found to have echocardiographic findings of endocarditis and underwent replacement of the conduit, as well as removal of vegetation from her right atrium. Subsequent to the re-operation, she manifested multi-organ failure and required respiratory oscillation. Despite increased support, she remained refractory to treatment. After discussion with her family, support was withdrawn.

Cox regression analysis

Cox regression analysis was conducted with all variables being found not to be predictive of bacteraemia. Although splenic anatomy was significant in the univariate analysis, it lost significance in the multivariate model ($p = 0.124$).

Discussion

So-called "heterotaxy" is a complex syndrome, which goes beyond simple discordance in sidedness. The essence of its cardiac manifestations is isomerism of the atrial appendages, but the issues of management extend far beyond the anatomical features. Multiple systems of organs are affected, both anatomically and functionally, particularly the immune system. Splenic anatomy can vary from a normally located spleen in the minority to the extremes of multiple or absent spleens.[2] Splenic function, moreover, may be compromised with any form of splenic anatomy, and thus all patients with isomerism are at increased risk for bacterial infections, thrombocytosis, and thromboembolism.[10,11] Gross structural abnormalities in the spleen as well as microscopic changes in the ultrastructure and function of splenic cilia are postulated to be causally responsible for splenic dysfunction.[7,9,28]

The risk of major infection was quantified in a large multicentric study of over 30,000 children undergoing cardiac surgery. The aim was to determine risk factors for infection, with a prevalence of 13.3% found in those deemed to be at major risk of infection.[29] This group of patients included those who were younger than 90 days, had a preoperative stay of more than 1 day, required preoperative ventilatory support, and had a genetic abnormality. This prevalence was lower than the prevalence of bacteraemia noted in one-fifth of our cohort. It is similar, however, to the prevalence noted in other studies.[30,31] A more recent study, not limited to patients with isomerism, but including 95 patients with isomerism, showed that one-third of the latter patients had an episode of nosocomial severe bacterial infection. Our findings indicate that neither splenic anatomy nor arrangement of the other abdominal organs have any impact on the rates of bacteraemia.

Median age at discovery of bacteraemia in our cohort was 4 months. A majority of the infectious events reported by others also occurred before 1 year of age. The latest instance of bacteraemia in our cohort occurred when the patient was 15 years of age, again being consistent with previous studies.[29,30,32] Studies characterising infections in those with either surgical or post-traumatic splenectomies have found that a majority of infections happened within 3 years following splenectomy, although there are some reports of infection after an interval of 65 years. Overall, nonetheless, it is younger patients with isomerism who are at greater risk for bacterial infections.[33,34]

In all, two-thirds of our patients were receiving prophylactic antibiotics, specifically amoxicillin. There are no current guidelines dictating the use of prophylactic antibiotics in patients with isomerism. Prophylaxis, however, seems reasonable in this population, as those with splenic dysfunction have a 600-fold increase in the risk of mortality from infection, with overall mortalities as high as 40 to 70%.[33,35–38] Mortality in our cohort was lower than that previously reported, at 12%, but this may be due to the higher rate of prophylaxis when compared with some of the previous studies. Of the two patients who died in our cohort from bacteraemia, one had asplenia, whereas the other had multiple spleens. Both patients, nonetheless, were receiving prophylaxis. The effectiveness of prophylaxis in the population of isomeric patients, therefore, remains unclear.

Additional data from the sickle cell population may be significant in this regard. These investigations have demonstrated decreases in both morbidity and mortality subsequent to antibiotic prophylaxis, particularly when started before 4 months of age – for example, results from the Prophylaxis with Oral Penicillin in Children with Sickle Cell Anemia trial demonstrated a reduction of nearly 85% in septicaemia due to *Streptococcus pneumoniae* subsequent

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to the use of prophylactic penicillin.[39] A follow-up study, also in sickle cell patients, then demonstrated that prophylaxis could safely be stopped at 5 years of age.[40] In our experience, four-fifths of all episodes of bacteraemia occurred in patients younger than 5 years of age. With regard to the four episodes of bacteraemia occurring after the age of 5 years, two patients were receiving antibiotic prophylaxis at the time of the episode, whereas two were not receiving antibiotic prophylaxis.

It seems reasonable, therefore, to use these data when considering the fate of patients with isomerism until specific data are available for the latter group. Patients with sickle cell disease also suffer from splenic dysfunction, making these two populations comparable from the stance of immunocompromise. Our data demonstrate that, in the setting of a relatively high incidence of prophylaxis, at 70%, bacteraemia is caused by encapsulated organisms ~20% of the time compared with other studies. Of the organisms cultured in our cohort, about one-third were susceptible to amoxicillin, one-sixth generally had intermediate susceptibility to amoxicillin, and half were resistant to amoxicillin.

Reports have indicated that antibiotic prophylaxis has altered the epidemiology of postoperative infections, such that the responsible organisms are resistant to usual therapy, leading to infections that are more difficult to treat. Although rates of bacterial infections were found to decrease, however, mortality was unaffected. This almost certainly reflects the resistance of the responsible organisms, which are therefore more difficult to treat.[41,42]

To date, it is usually splenic anatomy that has dictated the clinical management of children with isomerism with respect to infectious concerns. It is now well established that, however, patients with multiple spleens, or even those with solitary and normally located spleen in the setting of isomerism, may have functional asplenia.[9] Thus, it is surely wiser to base decisions regarding the risk of infection on knowledge of splenic function. This can be assessed by means of Howell–Jolly bodies or pitted red blood cells.[43–46] These tests, nonetheless, can be less than reliable earlier in life, and assessment can be difficult at ages younger than 2 years.[47] Establishment of normal splenic function at this time can permit the discontinuance of prophylactic antibiotics, but those with functional asplenia should continue to receive prophylaxis until 5 years of age. It is also important to ensure that children with functional asplenia remain properly vaccinated.[48] *Pneumococcal* and *Haemophilus influenzae* b vaccinations were more available during our study period than previous studies, which may also account for lower rates of bacteraemia and mortality.

A limitation of our study, and indeed the majority of other previous studies, is that splenic function is most often not tested in patients with isomerism. It is well known that those with multiple spleens, and even those with a solitary and normally located spleen, may have functional asplenia. We found functional asplenia in the majority of our individuals with bacteraemia. Thus, care providers must be aware of the risk of functional asplenia in these populations, and that the children may benefit from antibiotic prophylaxis. Serial evaluation of splenic function may help guide the need for the requirement of antibiotic prophylaxis in these patients, and avoid the overuse of prophylaxis. All of this, however, is conjecture and demonstrates the need for additional studies in this population. Another limitation is that we did not look at specific immune cell subsets. A recent study by Chiu et al demonstrated that low number of IgM memory B cells is an independent risk factor for infection in those with isomerism, but we were unable to study this effect as we do not routinely characterise immune cell populations.[49]

The strengths of our study include the assessment of a large number of patients over a long period of follow-up, as well as a complete description of the types of bacteria and their antibiotic susceptibilities. The inclusions of detailed phenotypic variations in splenic and visceral anatomy are important and also novel. The major limitations of the study are its retrospective nature and the low number of patients.

Conclusion

The risk of bacteraemia in patients with isomerism is not confined to those with asplenia. Somewhat surprisingly, we found it to be more prevalent in our cohort in those known to have multiple spleens. Cardiac anatomy, abdominal anatomy, and the use of antibiotic prophylaxis do not appear to alter this risk. Functional assessment of the immunological splenic status may provide better future stratification of risk.

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None. **Authors contributions:** R.S.L., A.P., and R.A. designed the study. R.S.L. collected and analysed the data and wrote the manuscript. A.P. and R.A. reviewed the data and wrote the manuscript.

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Conflicts of Interest

None.

Ethical Standards

As described in the methods, this study complies with the Helsinki Declaration and was approved by the local institutional review board.

References

1. Loomba RS, Hlavacek AM, Spicer DE, Anderson RH. Isomerism or heterotaxy: which term leads to better understanding? Cardiol Young 2015; 25: 1–7.
2. Uemura H, Ho SY, Devine WA, Anderson RH. Analysis of visceral heterotaxy according to splenic status, appendage morphology, or both. Am J Cardiol 1995; 76: 846–849.
3. Jacobs JP, Anderson RH, Weinberg PM, et al. The nomenclature, definition and classification of cardiac structures in the setting of heterotaxy. Cardiol Young 2007; 17 (Suppl 2): 1–28.
4. Loomba R, Shah PH, Anderson RH. Fetal magnetic resonance imaging of malformations associated with heterotaxy. Cureus 2015; 7: e269.
5. Loomba RS, Chandrasekar S, Shah PH, Sanan P. The developing role of fetal magnetic resonance imaging in the diagnosis of congenital cardiac anomalies: a systematic review. Ann Pediatr Cardiol 2011; 4: 172–176.
6. Loomba RS, Pelech AN, Shah PH, Anderson RH. Determining bronchial morphology for the purposes of segregating so-called heterotaxy. Cardiol Young 2015; 26: 1–13.
7. Loomba RS, Ahmed MM, Spicer DE, Backer CL, Anderson RH. Manifestations of bodily isomerism. Cardiovasc Pathol 2016; 25: 173–180.
8. Loomba RS, Shah PH, Anderson RH. Radiologic considerations in heterotaxy: the need for detailed anatomic evaluation. Cureus 2016; 8: 1–12.
9. Nagel BH, Williams H, Stewart L, Paul J, Stumper O. Splenic state in surviving patients with visceral heterotaxy. Cardiol Young 2005; 15: 469–473.
10. Yamamura K, Joo K, Ohga S, et al. Thrombocytosis in asplenia syndrome with congenital heart disease: a previously unrecognized risk factor for thromboembolism. Int J Cardiol 2013; 167: 2259–2263.
11. Loomba RS, Anderson RH. Letter to the editor regarding "situs inversus with levocardia, infrahepatic interruption of the inferior vena cava, and azygos continuation: a case report". Surg Radiol Anat 2015; 37: 1289–1290.
12. Loomba R. Thrombocytosis in the setting of isomerism and a functionally univentricular heart. Cureus 2015; 7: 1–10.
13. Koudieh M, McKenzie ED, Fraser CD Jr. Outcome of Glenn anastomosis for heterotaxy syndrome with single ventricle. Asian Cardiovasc Thorac Ann 2006; 14: 235–238.
14. Loomba RS. Arterial desaturation due to pulmonary arteriovenous malformations after the Kawashima. Ann Pediatr Cardiol 2015; 9: 1–4.
15. Loomba RS, Aggarwal S, Arora RR, Anderson R. Bodily isomerism is an independent risk factor for pulmonary hypertension in adults with congenital heart disease. Ther Adv Respir Dis 2016; 10: 104–199.
16. Loomba RS, Willes RJ, Kovach JR, Anderson RH. Chronic arrhythmias in the setting of heterotaxy: differences between right and left isomerism. Congenit Heart Dis 2015; 11: 7–18.
17. Loomba RS, Aggarwal S, Gupta N, et al. Arrhythmias in adult congenital patients with bodily isomerism. Pediatr Cardiol 2015; 37: 1281–1287.
18. Bartz PJ, Driscoll DJ, Dearani JA, et al. Early and late results of the modified fontan operation for heterotaxy syndrome 30 years of experience in 142 patients. J Am Coll Cardiol 2006; 48: 2301–2305.
19. Loomba RS, Nijhawan K, Anderson R. Impact of era, type of isomerism, and ventricular morphology on survival in heterotaxy: implications for therapeutic management. World J Pediatr Congenit Heart Surg 2016; 7: 54–62.
20. Wu MH, Wang JK, Lue HC. Sudden death in patients with right isomerism (asplenism) after palliation. J Pediatr 2002; 140: 93–96.
21. Katcher AL. Familial asplenia, other malformations, and sudden death. Pediatrics 1980; 65: 633–635.
22. Sadiq M, Stumper O, De Giovanni JV, et al. Management and outcome of infants and children with right atrial isomerism. Heart 1996; 75: 314–319.
23. Kanthan R, Moyana T, Nyssen J. Asplenia as a cause of sudden unexpected death in childhood. Am J Forensic Med Pathol 1999; 20: 57–59.
24. Song J, Kang IS, Huh J, et al. Interstage mortality for functional single ventricle with heterotaxy syndrome: a retrospective study of the clinical experience of a single tertiary center. J Cardiothorac Surg 2013; 8: 93.
25. Gentles TL, Mayer JE Jr, Gauvreau K, et al. Fontan operation in five hundred consecutive patients: factors influencing early and late outcome. J Thorac Cardiovasc Surg 1997; 114: 376–391.
26. Knott-Craig CJ, Danielson GK, Schaff HV, Puga FJ, Weaver AL, Driscoll DD. The modified Fontan operation. An analysis of risk factors for early postoperative death or takedown in 702 consecutive patients from one institution. J Thorac Cardiovasc Surg 1995; 109: 1237–1243.
27. Humes RA, Feldt RH, Porter CJ, Julsrud PR, Puga FJ, Danielson GK. The modified Fontan operation for asplenia and polysplenia syndromes. J Thorac Cardiovasc Surg 1988; 96: 212–218.
28. Rodin AE, Sloane JA, Nghiem QX. Polysplenia with severe congenital heart disease and Howell-Jolly bodies. Am J Clin Pathol 1972; 58: 127–134.
29. Barker GM, O'Brien SM, Welke KF, et al. Major infection after pediatric cardiac surgery: a risk estimation model. Ann Thorac Surg 2010; 89: 843–850.
30. Waldman JD, Rosenthal A, Smith AL, Shurin S, Nadas AS. Sepsis and congenital asplenia. J Pediatr 1977; 90: 555–559.
31. Prendiville TW, Barton LL, Thompson WR, Fink DL, Holmes KW. Heterotaxy syndrome: defining contemporary disease trends. Pediatr Cardiol 2010; 31: 1052–1058.
32. Chiu SN, Shao PL, Wang JK, et al. Severe bacterial infection in patients with heterotaxy syndrome. J Pediatr 2014; 164: 99–104; e101.
33. Bisharat N, Omari H, Lavi I, Raz R. Risk of infection and death among post-splenectomy patients. J Infect 2001; 43: 182–186.
34. Hansen K, Singer DB. Asplenic-hyposplenic overwhelming sepsis: postsplenectomy sepsis revisited. Pediatr Dev Pathol 2001; 4: 105–121.
35. Lynch AM, Kapila R. Overwhelming postsplenectomy infection. Infect Dis Clin North Am 1996; 10: 693–707.
36. Singer DB. Postsplenectomy sepsis. Perspect Pediatr Pathol 1973; 1: 285–311.
37. Holdsworth RJ, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. Br J Surg 1991; 78: 1031–1038.
38. Brigden ML, Pattullo AL. Prevention and management of overwhelming postsplenectomy infection – an update. Crit Care Med 1999; 27: 836–842.
39. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. New Engl J Med 1986; 314: 1593–1599.
40. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. Prophylactic Penicillin Study II. J Pediatr 1995; 127: 685–690.
41. Classen DC, Evans RS, Pestotnik SL, Horn SD, Menlove RL, Burke JP. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. New Engl J Med 1992; 326: 281–286.
42. Siegel JD, McCracken GH Jr, Threlkeld N, Milvenan B, Rosenfeld CR. Single-dose penicillin prophylaxis against neonatal group B streptococcal infections. A controlled trial in 18738 newborn infants. New Engl J Med 1980; 303: 769–775.

43. Crosby WH. Hyposplenism: an inquiry into normal functions of the spleen. Annu Rev Med 1963; 14: 349–370.
44. McCarthy CF, Fraser ID, Evans KT, Read AE. Lymphoreticular dysfunction in idiopathic steatorrhoea. Gut 1966; 7: 140–148.
45. Harrod VL, Howard TA, Zimmerman SA, Dertinger SD, Ware RE. Quantitative analysis of Howell-Jolly bodies in children with sickle cell disease. Exp Hematol 2007; 35: 179–183.
46. Corazza GR, Ginaldi L, Zoli G, et al. Howell-Jolly body counting as a measure of splenic function. A reassessment. Clin Lab Haematol 1990; 12: 269–275.
47. Combs LS, Gupta S, Mehta A. Evaluation of spleen in children with heterotaxia and congenital heart disease. Tennessee medicine. J Tenn Med Assoc 2004; 97: 161–163.
48. Committee on Infectious Diseases American Academy of Pediatrics. Red Book: 2006 Report of the Committee on Infectious Diseases. Committee on Infectious Diseases American Academy of Pediatrics, Philadephia, Pennsylvania, 2006.
49. Chiu SN, Shao PL, Wang JK, et al. Low immunoglobulin M memory B-cell percentage in patients with heterotaxy syndrome correlates with the risk of severe bacterial infection. Pediatr Res 2015; 70: 271–277.

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