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Research Article

Risk of Noncardiac Infection in Adult Congenital Heart Disease Patients with Isomerism (Heterotaxy): Frequency, Significance of Age and Causative Organisms

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Abstract

Background: Heterotaxy, better referred to as bodily isomerism, has long been associated with increased risk of infectious outcomes, particularly bacteremia. This has been understood to be in part mediated by functional asplenia. The risk in adults is not as well understood and thus we set forth to study noncardiac infectious outcomes from a predominantly adult database and try to determine risk factors for bacteremia.

Methods: Patients were identified in the Nationwide Inpatient Sample (NIS) as having isomerism or not. Infectious outcomes were also identified as were other patient characteristics. Chi squared analysis was done to determine factors associated with isomerism. Next, a binomial logistic regression was done to identify risk factors for bacteremia and determine if isomerism is such a risk factor.

Results: A total of 6,907,109 million admissions were included in this analysis, 861 of which had isomerism. Those with isomerism were more likely to develop upper respiratory infections and bacteremia by univariate analysis. A logistic regression identified isomerism as an independent risk factor, increasing the odds of bacteremia by 240% while asplenia increased the odds by 300%. Those with isomerism tended to have bacteremia at a much younger age, generally in childhood.

Conclusion: Isomerism is associated with increased odds of upper respiratory infection and bacteremia. Isomerism is an independent risk factor for bacteremia which most frequently occurs during childhood in those with isomerism. Asplenia is also an independent risk factor for bacteremia.

Keywords: *Bacteremia; Sepsis; Septic Shock; Encapsulated Bacteria; Isomerism; Heterotaxy; Laterality; Spleen; Polysplenia; Asplenia; Prophylactic Antibiotics*

Abbreviations

NIS: Nationwide Inpatient Sample; ICD: International Classification of Disease

Introduction

Bodily isomerism, also known as heterotaxy, is characterized by the finding of isomerism, as opposed to the anticipated lateralization, in the various systems of organs [1]. Once segregated based on splenic anatomy, it is now appreciated that a better cardiac discriminant,

is the atrial appendage morphology, which demonstrate either morphologically right or left features bilaterally [2,3]. Appendage isomerism, usually matched by bronchial isomerism and jumbled-up abdominal organs, and hereafter to be referred to simply as isomerism, is frequently associated with complex intracardiac malformations requiring functionally univentricular palliation [4,5]. Additionally, these patients are at risk for arrhythmias due to malformations of the cardiac conduction system [6-8]. Gastrointestinal malformations of the gastrointestinal system such as malrotation and tracheoesophageal fistula, may also be present. The immune system can also be compromised, most noticeably manifested by the presence of multiple spleens, or the absence of a spleen [1,2,4,5].

All of the splenic malformations anticipated in the setting of isomerism have functional implications, as those with multiple spleens, or even a solitary and normally located spleen, may have functional asplenia [9,10]. All the patients with functional asplenia are known to be at greater risk of bacteremia, particularly from encapsulated organisms [11,12]. Additionally, children with isomerism are more likely to require longer stays in the intensive care unit subsequent to surgery, with the need for intubation and indwelling catheters, which further compound the risks [13,14]. All of these complications occur in the setting of an increased likelihood of ciliary dyskinesia, which may mediate some of the increased risks of infection. A majority of this increased risk for infection occurs in the first 5 years of life, although the risk later in life has not been well investigated. With this in mind, we used the Nationwide Inpatient Sample (NIS) to characterize the risk of various noncardiac infections in patients known to exhibit isomerism, comparing this risk to those with usual arrangement of the organs, so-called situs solitus.

Methods

Identification of patients

Data regarding hospital admissions was obtained from the 2012 NIS, which is the most recent iteration of the database. The NIS is a database of hospital admissions designed to capture 20% of all admissions in the United States. The NIS is designed primarily to capture adult admissions as data from pediatric institutions are collected elsewhere. Patients with isomerism were identified using the International Classification of Diseases, Ninth Revision (ICD-9) code 746.87. Patients with mirror-imaged arrangement, so-called situs inversus, were not included in this group, since if patients are correctly diagnosed, the organs remain lateralized in this setting. Admissions associated with bacteremia were identified using the ICD-9 code of 790.7, sepsis by the code 995.91, and septic shock by the code 785.52.

We identified additional reported infections using code 599.0 for involvement of the urinary tract, 465.9 for upper respiratory infection, 486 for pneumonia, and 322.9 for meningitis. Bacterial organisms causing septicemia were identified using the code 038.0 for streptococcal septicemia, 038.10 for staphylococcal septicemia, 038.2 for pneumococcal septicemia, 038.41 for *Haemophilus influenzae* septicemia, 038.42 for *Escherichia coli* septicemia, 038.43 for Pseudomonal septicemia, and 036.2 for meningococcal septicemia.

Identification and collection of data

Demographic information, including gender and race, were collected for each reported admission. We also collated characteristics such as month of admission, and length and cost of stay, as well as information regarding comorbid conditions. In this respect, we identified hyperlipidemia using codes 272.0, 272.1, 272.2 and 272.3, hypertension using 401.0, 401.1 and 401. Overweight or obese patients were identified using codes 278.00, 278.01 and 278.02, with current smokers being identified using code 305.1.

Collected data of interest regarding isomerism included cardiac anatomy, as well splenic anatomy. We identified congenital cardiac malformations commonly associated with isomerism using code 745.6 for those with a functionally univentricular hearts, 745.11 for double outlet right ventricle, 745.6 for atrioventricular septal defect, 747.42 for partially anomalous pulmonary venous connections, and 747.41 for totally anomalous pulmonary venous connection. Absence of the spleen, or presence of multiple spleens, was collected using 759.0. The codes available using ICD-9 do not permit the distinction between patients lacking a spleen, as opposed to those having multiple spleens.

Statistical analysis

Continuous variables are reported using mean and standard deviations, while categorical variables are reported using absolute frequencies and percentages. We analysed continuous variables using Student's t-test, or the Mann-Whitney-U test, as appropriate, with categorical variables analyzed using chi-squared calculations. Baseline characteristics, such as age, gender, race, and comorbid conditions were compared between those deemed to have isomerism and those with usual arrangement of the organs. We used univariate cross tabulation analysis to determine the odds of having specific arrhythmias in those deemed to have isomerism. We then performed multivariate logistic regression, using bacteremia as the dependent variable, and age, gender, race, isomerism, functional asplenia, and various congenital cardiac malformations, as the independent variables. All statistical analysis was done utilizing SPSS Version 20.0 (Chicago, IL).

Results

Overall characteristics

We were able to include 6,907,109 admissions in our analysis, from which we deemed 861 (0.01%) to have occurred in the setting of isomerism. The average age at admission did not significantly different between those considered to have isomerism as opposed to usually arranged organs. Length and cost of hospitalization tended to be greater in those with isomerism, with these patients also significantly less likely to report current smoking (5.8% vs 12.9%), and to have a decreased frequency of diabetes mellitus (9.9% vs 21.9%), obesity (6.4% vs 10.5%), hypertension (18.4% vs 34.6%), and hyperlipidemia (2.2% vs 5.0%).

Not surprisingly, congenital cardiac malformations were more commonly associated with the presence of isomerism. Functionally univentricular hearts were documented in 7.8% of patients with isomerism, doublet outlet right ventricle in 9.9%, tetralogy of Fallot in 1.4%, ventricular septal defect in 9.2%, and oval fossa defects in 14.6%. Partially anomalous pulmonary venous connections were reported in 1.3% of those with isomerism, while totally anomalous pulmonary venous connection was reported in 1.7%. In this respect, the definitions used for identifying the presence of anomalous pulmonary venous connections was not specified, and likely differed from institution to institution. Those with right isomerism, by definition, will all have totally anomalous pulmonary venous connection, even when the pulmonary veins return to the heart, showing that the documented numbers grossly underrepresent the true frequency of this finding. Inpatient mortality was 2.9% in those reported to have bacteremia in the setting of isomerism, compared to zero in those with usually arranged organs (p = 0.566) (Table 1).

	No isomerism (n = 6,906,248)	Isomerism (n = 861)	p-value
Age at admission (years)	51.28 ± 25.82	25.49 ± 30.21	< 0.0001
Female	4,007,523 (58.0)	379 (44.0)	< 0.0001
Current smoker	888,276 (12.9)	50 (5.8)	< 0.0001
Hyperlipidemia	348,536 (5.0)	19 (2.2)	< 0.0001
Hypertension	2,386,574 (34.6)	158 (18.4)	< 0.0001
Diabetes mellitus	1,509,816 (21.9)	85 (9.9)	< 0.0001
Acute kidney injury	629,878 (9.1)	56 (6.5)	0.008
Chronic kidney disease	812,138 (11.8)	63 (7.3)	< 0.0001
Overweight or obese	724,704 (10.5)	55 (6.4)	< 0.0001
Obstructive sleep apnea	302,485 (4.4)	28 (3.3)	0.106
Race			< 0.0001
White	4,360,026 (66.9)	447 (56.2)	
Black	967,372 (14.8)	97 (12.2)	
Hispanic	742,364 (11.4)	172 (21.6)	
Asian or Pacific Islander	168,044 (2.6)	30 (4.4)	
Native American	47,063 (0.7)	11 (0.8)	
Other	236,681 (3.6)	38 (4.8)	
Length of hospital stay	4.65 ± 6.73	11.39 ± 25.90	< 0.0001
In-hospital mortality	133,994 (1.9)	45 (5.2)	< 0.0001
Myocardial infarction	172,377 (2.5)	17 (2.0)	0.327
Functionally univentricular	347 (0.1)	67 (7.8)	< 0.0001
Double outlet right ventricle	546 (0.1)	85 (9.9)	< 0.0001
Atrioventricular septal defect	807 (0.1)	65 (7.5)	< 0.0001
Partial anomalous venous connection	196 (0.1)	11 (1.3)	< 0.0001
Total anomalous venous connection	236 (0.1)	15 (1.7)	< 0.0001
Absence of a spleen or presence of multiple spleens	687 (0.1)	39 (4.5)	< 0.0001
Tetralogy of fallot	1,414 (0.1)	12 (1.4)	< 0.0001
Ventricular septal defect	7,525 (0.1)	79 (9.2)	< 0.0001
Secundum atrial septal defect	29,410 (0.4)	126 (14.6)	< 0.0001

Table 1: *Characteristics of hospitalizations for those with and without isomerism.*

Infectious endpoints in those with and without isomerism

Univariate analysis showed Isomerism to be associated with an increased risk of bacteremia, with an odds ratio of 2.049, and 95% confidence interval from 1.130 to 3.174) (Table 2). Bacteremia was noted with a frequency of 1.3% in those with isomerism. The average age of those reported with bacteremia was significantly lower in those with isomerism, at 8.64 as opposed to 58.74 years ($p < 0.0001$). The length and cost of hospitalizations associated with bacteremia were also greater in those with isomerism, at 53.45 in contrast to 10.22 days, and 85,899.61 as opposed to 637,800.18 US dollars ($p < 0.0001$ - Table 3).

	No isomerism (n = 6,906,248)	Isomerism (n = 861)	Odds ratio (Odds ratio and 95% confidence interval)	p-value
Urinary tract infection	564,301 (8.2)	40 (4.6)	0.548 (0.399 to 0.752)	< 0.0001
Upper respiratory infection	34,714 (0.5)	16 (1.9)	3.748 (2.285 to 6.147)	< 0.0001
Pneumonia	424,866 (6.2)	55 (6.4)	1.041 (0.792 to 1.368)	0.773
Meningitis	2,275 (0.1)	0 (0)	--	0.594
Bacteremia	43,343 (0.6)	11 (1.3)	2.049 (1.130 to 3.714)	0.016
Sepsis	166,043 (2.4)	17 (2.0)	0.818 (0.506 to 1.322)	0.410
Septic shock	72,932 (1.1)	12 (1.4)	1.324 (0.749 to 2.341)	0.322
Streptococcal septicemia	13,487 (0.2)	#	1.190 (0.297 to 4.766)	0.806
Staphylococcal septicemia	1866 (0.1)	0 (0)	--	0.630
Pneumococcal septicemia	3,245 (0.1)	0 (0)	--	0.524
Hemophilus influenzae septicemia	427 (0.1)	0 (0)	--	0.818
Escherichia coli septicemia	22,763 (0.3)	#	0.704 (0.176 to 2.820)	0.618
Pseudomonal septicemia	4,308 (0.1)	#	1.863 (0.262 to 13.243)	0.528
Meningococcemia	65 (0.1)	0 (0.0)	--	0.928

Table 2: *Frequency of infectious occurrences in those with and without isomerism.*

 # less than 10, number cannot be specified per database restrictions

	No isomerism (n = 43,343)	Isomerism (n = 11)	p-value
Age (years)	58.74 ± 22.22	8.64 ± 17.40	< 0.0001
Length of stay (days)	10.22 ± 13.47	53.45 ± 71.26	< 0.0001
Cost of admission (US dollars)	85,899.61 ± 164,235.61	637,800.18 ± 979,719.31	< 0.0001
Death	1260 (2.9)	0 (0)	0.566

Table 3: *Characteristics of admissions associated with bacteremia in those with and without isomerism.*

The risk of septicemia and septic shock, in contrast, did not differ between the two groups, nor did we identify any difference in the reported bacterial organisms causing septicemia. The frequency of infections of the upper respiratory tract was greater in those with isomerism, but the frequency of urinary tract infections was lower. Reports of pneumonia and meningitis did not differ between the two groups (Table 4).

	No bacteremia (n = 822)	Bacteremia (n=39)	p-value
Age (years)	51.28 ± 25.82	28.74 ± 27.19	< 0.0001
Length of stay (days)	4.65 ± 6.73	8.37 ± 13.95	< 0.0001
Cost of admission (US dollars)	38,540.32 ± 70,466.63	97,813.86 ± 208,253.08	< 0.0001
Death	44 (5.4)	#	0.445

Table 4: *Characteristics of admissions between isomerism patients with and without bacteremia.*

 # less than 10, number cannot be specified per database restrictions

Multivariate regression analysis for bacteremia

This analysis showed presence of isomerism to increase the risk of bacteremia by 240%. Other independent risk factors for bacteremia included greater age, male gender, race, presence of functional asplenia, and presence of a double outlet right ventricle. The risk of bacteremia increased 1.3% with each year of age, was 35% greater in males, was 300% greater in those deemed to have functional asplenia, and was 140% greater in those with double outlet right ventricle.

Discussion

Our analysis of a cohort of patients largely made up of adults requiring an inpatient admission showed that the presence of isomerism, as opposed to usually arranged organs, carries an increased risk for the development of bacteremia. This risk is greater at a younger age and is associated with hospitalizations that are both greater in length and cost. Hospitalizations associated with bacteremia tended to be 5 times longer in those with isomeric arrangement of the organs, and were 7 times more costly.

The age at the occurrence of bacteremia is likely lower for several reasons. Firstly, congenital cardiac malfunctions associated with isomerism often require surgical intervention in the first few years of life [15]. Children undergoing cardiac surgery are likely to be inpatients for several days, with hospital stay in and of itself being associated with an increased risk of bacteremia. Admissions associated with cardiac surgery are also likely to extend over several days, many of which will entail the presence of invasive monitoring lines, a feature also associated with increased risk of bacteremia. The risk of bacteremia, furthermore, is greater in those with functional asplenia, with this risk being greatest in the early years of life [11,12,16-19]. Presumably as these patients grow older, immunizations along with other factors mitigate the risk of bacteremia, at least through young adulthood. Previous studies made up of cohorts of children known to have isomerism have demonstrated the mean age of bacteremia as being between 4 and 12 months of age [20,21]. As we have already emphasized, the length of hospital stay is likely to be longer in those with isomerism. For those patients undergoing complex palliative surgeries, the length of stay can already be lengthy, and is then increased by the presence of bacteremia. It is intuitive that such longer admissions would be associated with greater cost, and that admissions associated with cardiac surgery would also be costlier.

Although bacteremia was more frequent in those deemed to have isomerism, we failed to identify any increase in the frequency of sepsis or septic shock. This may be due to earlier detection and treatment of bacteremia in those with isomerism, particularly since many of these patients seem to have had bacteremia while already in the hospital. Specific organisms associated with septicemia also did not differ between those with and without isomerism. We were able to capture data reporting several encapsulated organisms, including *Neisseria meningitis, Streptococcus pneumoniae and Haemophilus influenza*. Those with isomerism did not demonstrate a higher risk of septicemia secondary to infection by such encapsulated bacteria, despite the known increased risk produced by functional asplenia. This may be because of the use of prophylactic antibiotics in those known to exhibit isomerism [22], although we were unable to capture the data needed to validate this hypothesis.

Presence of isomerism, therefore, is associated with an increased risk of bacteremia, with a larger burden of this risk being in childhood. Use of prophylactic antibiotics, patient and family education regarding immunizations, inpatient and family education regarding febrile illnesses, and development of protocols for evaluating and managing patients with isomerism thus all become particularly important. Our findings also demonstrate why prompt deescalation of care in the postoperative setting is also important, specifically in regards to removal of invasive lines. Our study has provided an estimate of the prevalence of infections in those deemed to have isomerism, particularly in the older population. The overall frequency of bacteremia, nonetheless, was lower when compared to studies of children, since the cohort captured by NIS primarily consists of adults. A previous study demonstrated a prevalence of bacteremia of 27% in those with isomerism. Length of follow-up in this study was a total of 587 patient-years, with a mean follow-up of 7.0 years per patient. No significant independent variables were found to be significantly associated with bacteremia after multivariate analysis, which included both absence of the spleen and presence of multiple spleens. When compared to such previous studies, our analysis is able to demonstrate a more longitudinal assessment of bacteremia and other infectious outcomes. This risk can also be compared to that for the general population by use of the NIS and can also be evaluated to identify independent risk factors as was done.

Our analysis is not without its limitations. Firstly, we were unable to segregate patients into the subsets of right as opposed to left isomerism. Additionally, the coding available for congenital cardiac malformations in ICD-9 is less than ideal in terms of extraction of precise information regarding cardiac anatomy. It was also impossible to capture the precise arrangement of the abdominal organs.

All of this will hopefully change with the appearance of ICD-10, and will certainly be possible when ICD-11 is completed.

In conclusion, we have shown that patients with an Isomeric arrangement of the organs carry an increased risk of bacteremia but not sepsis, with this risk being the greatest in childhood. Causative bacterial organisms did not differ between those with isomerism as compared to those with usual arrangement of the organs. The length and cost of hospital stays, nonetheless, is greater for those having admissions associated with bacteremia in the setting of isomerism.

Conclusion

Isomerism is associated with increased odds of upper respiratory infection and bacteremia. Isomerism is an independent risk factor for bacteremia which most frequently occurs during childhood in those with isomerism. Asplenia is also an independent risk factor for bacteremia.

Competing Interest

The authors declare that they have no competing interests.

Authors' Contributions

Rohit Loomba: Study design, data analysis, preparation of initial draft, revision of manuscript.
Conor Kriz: Study design, review of data analysis, revision of manuscript.
Matthew Buelow: Review of data analysis, revision of manuscript.
Salvatore Aiello: Study design, data analysis, revision of manuscript.
Robert Anderson: Review of data analysis, revision of manuscript.

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