Severe Bacterial Infection in Patients with Heterotaxy Syndrome

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Objective To determine the incidence of sepsis in patients with heterotaxy syndrome.

Study design From our institutional database, we identified patients with heterotaxy syndrome and other complex congenital heart disease (CHD) born between 2001 and 2011. Severe bacterial infection was defined as sepsis with positive culture result or infection with abscess formation.

Results We enrolled 95 patients with heterotaxy syndrome (88 with right atrial isomerism and 7 with left atrial isomerism) and 142 patients with complex CHD. With 1026 person-years follow-up, the 5-year survival was 52% and 65.7% in heterotaxy and complex CHD groups, respectively ($P = .239$). Community-acquired severe bacterial infection occurred only in heterotaxy syndrome (13 episodes in 10 patients, 3 of whom had spleen noted at imaging study) with 2- and 5 years cumulative severe bacterial infection rate of 9.6% and 14.5%, respectively. The overall mortality rate of those with community-acquired severe bacterial infection was 31%. Pneumococcus and *Citrobacter freundii* were the most common pathogens. Nosocomial severe bacterial infection occurred in 33.3% of all patients and 12.5% of all procedures. The rates (0.59 and 0.52/100 hospitalization days in heterotaxy and complex CHD group) and the pathogens of nosocomial severe bacterial infection were similar between heterotaxy and complex CHD groups.

Conclusions Patients with heterotaxy syndrome are at high risk for community-acquired severe bacterial infection and also have high mortality rate whether the spleen is present or not. The risk of nosocomial severe bacterial infection seems similar to that of patients with other complex CHD. *(J Pediatr 2014;164:99-104)*.

Heterotaxy syndrome is a developmental defect that involves the thoracic and visceral organs. In these patients, paired organs, such as the lungs, tracheobronchial, heart, and visceral organs (stomach, liver, spleen, and gastrointestinal tract), often are mirror images instead of having the unique right and left asymmetry characteristics that are normally present. Heterotaxy can be further divided into right atrial isomerism (RAI) and left atrial isomerism (LAI) according to the morphology of the atrial appendage. Owing to associated abnormalities in the cardiac looping, complex congenital heart disease (CHD) is common in such patients.[1-8] Multistage surgery, such as the single ventricle physiology surgery (Fontan type operation), is a requisite for long-term survival. In our country, heterotaxy is not very rare, and the prevalence of RAI is much more common than LAI.[1,3,5,6]

The long-term survival rate in patients with heterotaxy syndrome still is not optimistic. The 5-year survival in our previous series was around 55%, which is significantly lower than that in other cyanotic CHDs.[2,7,9,10] In addition to surgery- and cardiac-related death, infection is an important cause of death. Infection accounted for 23% of unexpected death in our previous study.[2] As some of the cases of RAI are associated with agenesis of spleen, these patients are susceptible to severe infection, especially in early life.[1,2,11] However, the overall incidence of community-acquired and nosocomial sepsis in these patients is still unknown. We investigated the incidence of community- and nosocomially-acquired severe bacterial infection in patients with heterotaxy and compared such risk with cohort of patients with other complex CHD.

Methods

From January 2001 to December 2011, all patients born and diagnosed with heterotaxy syndrome in the National Taiwan University Hospital were identified. Patients with complex CHD who did not have associated heterotaxy syndrome served as controls. The definition of complex CHD in our study was CHD requiring single ventricle physiology surgery. Those with severe chromosomal anomaly including trisomy 13 and 18 were excluded from our study. The data collection

CHD	Congenital heart disease
CT	Computed tomography
LAI	Left atrial isomerism
RAI	Right atrial isomerism

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Table II. The associated visero-bronchial and systemic vein lateralization anomaly and extracardiac anomaly in the heterotaxy syndrome and complex CHD

	RAI n = 88	LAI n = 7	Complex CHD n = 142	*P* value
No spleen at image study	65 (77.4%)	1 (14.3%)	0	<.001
Bilateral superior vena cava	48 (54.5%)	4 (57.1%)	21 (14.8%)	<.001
Interrupted inferior vena cava	0	7 (100%)	0	<.001
Horizontal liver	73 (83.9%)	3 (42.9%)	0	<.001
Symmetry of tracheobronchial tree	79 (97.5%)	7 (100%)	3 (2.4%)	<.001
Extracardiac anomaly	21 (23.9%)	2 (28.6%)	14 (9.9%)	.011
Malrotation	9	1	1	
Hiatal hernia	7	0	2	
VATER association	1	0	3	
Multiple anomaly	1	0	3	
Genitourinary tract anomaly	1	0	1	
Gastrointestinal tract anomaly	2	1	1	
Others	3		3	

VATER, vertebrae, anus, trachea, esophagus, renal.

was in accordance with the regulation of the institutional review board policy in National Taiwan University Hospital. The diagnostic criteria of heterotaxy syndrome included bilateral atrial appendage morphology belonging to either right atrium or left atrium noted either by surgery or computed tomography (CT). The spleen status was defined according to the CT or abdominal sonography report, and tracheobronchial tree symmetry was analyzed using CT. Only patients receiving regular follow-up at our hospital were included.

We reviewed all medical records, culture results, and drug sensitivity data. The definition of severe bacterial infection includes clinical signs of sepsis plus: (1) positive blood culture with elevated white count or inflammation markers; (2) more than 2 sets of positive blood culture consecutively; (3) culture from the aseptic tissue fluid including cerebral spinal fluid and ascites; or (4) brain abscess, empyema, or other abscess formation requiring drainage. Community-acquired sepsis was defined as severe bacterial infection with positive culture result within 48 hours after admission and no prior interventions. Patients with clinical signs of sepsis who died within 24 hours after arriving at the hospital also were viewed as community-acquired sepsis even without positive blood culture result. Perinatal infection was defined as severe bacterial infection at <7 days of age.

The antibiotics prophylaxis guideline for heterotaxy syndrome in our country is "emergent empiric therapy," that is, antibiotics administered immediately if any infection signs or fever are noted by clinicians.[12] Antibiotics used are by physician choice. In addition, we also prescribe parenteral cefazolin prior to invasive interventions and surgical procedures.

We used Student *t* test for comparisons of numerical data and χ^2 test for comparisons of categorical data. Survival and cumulative incidence of infection were plotted using Kaplan–Meier method, and the log-rank test was used to compare the mean survival between 2 groups. Statistical significance was defined as a *P* value <.05.

Results

There were 253 patients identified, but we excluded 16 patients (13 patients with incomplete follow-up data at our hospital, and 3 patients with heterotaxy without associated CHD). Finally, 237 patients (male/female 134/103) were enrolled in our study: 88 patients with RAI (RAI group, male/female 53/35), 7 patients with LAI (LAI group, male/female 4/3), and 142 patients with complex CHD without heterotaxy (complex CHD group, male/female 77/65). Cardiac diagnosis was made by 2 months of age and is summarized in **Table I** (available at www.jpeds.com). The incidence of total anomalous pulmonary venous return was 100% in RAI, (65.9% was cardiac type, 17% was supracardiac type, 8% was infracardiac type, and 9.1% was mixed type). All infracardiac type, 80% of supracardiac type, 75% of mix type, and 3.4% of cardiac type total anomalous pulmonary venous return had pulmonary vein obstruction. Among these patients, 37 (15.6%) had associated extracardiac anomaly, which was higher in RAI and LAI groups than in the other complex CHD group (**Table II**). In patients with RAI, 77.4% had no spleen identified by imaging; the incidence was higher than patients with LAI and those with other complex CHD (**Table II**). Although most of the patients with RAI had bilateral trifurcated pattern of the tracheobronchial tree and bilateral trilobed lung, 3 of the patients had atrial tracheopulmonary situs discordance. In addition, atrial-visceral situs discordance was more common (ie, up to 14.9% in patients with heterotaxy syndrome).

Survival Analysis

After 1026 person-years follow-up, the 5-year survival rate was 52.0% and 65.7% in heterotaxy syndrome and other patients with complex CHD, respectively ($P = .239$; **Figure**, A). The cause of mortality is listed in **Table III**. Operation-related mortality was the major cause in our cohort,