



Journal Homepage: - [www.journalijar.com](http://www.journalijar.com)

## INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/12755

DOI URL: <http://dx.doi.org/10.21474/IJAR01/12755>



### RESEARCH ARTICLE

#### RIGHT SIDED ENDOCARDITIS: CASE SERIES FROM MOROCCO

A. Laalou, A. Chachi, A. Benbahia, S. Jourani, B. Zainab, G.F.I. Gildas, M. El Jamili, N. Charei, D. Benzeroual, S. El Karimi and M. El Hattaoui

Departement of Cardiology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech, Morocco.

#### Manuscript Info

##### Manuscript History

Received: 16 February 2021

Final Accepted: 19 March 2021

Published: April 2021

##### Key words:-

Infective Endocarditis, Right-Sided, Tricuspid Valve

#### Abstract

**Objective:** Compared with the extensive data on left sided infective endocarditis, right-sided infective endocarditis (RSIE) remains a rare condition. It accounts for 5–10% of all cases of infective endocarditis (IE) [1] [2] [3]. Although it is predominantly encountered in the injecting drug user (IDU) population, where HIV and HCV infections often coexist, rheumatic heart disease remains the most important predisposing factor for IE in our context.

The aim our study is to report clinical, investigation, management and outcome data in 5 patients diagnosed with RSIE in our department during the last 2 years.

**Methods:** A retrospective analysis of data of 5 patients with right sided endocarditis in a tertiary care center from 2018 to 2020 was done.

**Results:** All of our patients were young aged females; none of them had cardiac devices or history of drug use. Persistent fever was the most common clinical presentation. Interestingly, 4 patients presented clinical heart failure. 3 patients had isolated tricuspid valve IE, one patient had isolated pulmonary valve IE, and one patient have both tricuspid and pulmonary valve IE. Blood cultures were negative in two cases, whilst two others were positive to Streptococcus (alpha) and one positive to Staphylococcus. 4 patients underwent surgical treatment after well conducted antibiotic therapy; the indications were the presence of right heart failure secondary to severe tricuspid regurgitation and the size of the vegetations. Unfortunately, one patient died of massive pulmonary embolism despite well conducted antibiotherapy.

**Conclusion:** RSIE is rare and occurs in a wide range of underlying conditions like implantable electronic devices, indwelling catheters, CHD and immune compromised state. Surprisingly, it can occur in young individuals without known risk factors. In our context, rheumatic heart disease remains the most incriminated etiology which lead us to question three essential points:

1. The interest of antibiotic prophylaxis in young patients with VSDs
2. The use of empiric antibiotics with action against streptococcus
3. Early surgical treatment in rheumatic heart disease.

**Corresponding Author:- Dr. Laalou Ali**

Address:- Departement of Cardiology, Errazi Hospital, Mohammed VI University Teaching Hospital, Marrakech. Morocco.

### Introduction:-

Compared with the extensive data on left sided infective endocarditis, right-sided infective endocarditis (RSIE) remains a rare condition. It accounts for 5–10% of all cases of infective endocarditis (IE) (1–3). Although it is predominantly encountered in the injecting drug user (IDU) population, where HIV and HCV infections often coexist, congenital rheumatic heart disease remains the most important predisposing factor for IE in our context.

The clinical presentation is often a persistent fever with respiratory symptoms whilst signs of systemic embolization as seen in left-sided IE are notably absent. The diagnosis of IE is made based upon a synthesis of clinical, microbiological, and echocardiographic findings. The modified Duke criteria are the standard criteria used to guide the diagnosis of IE (1). The two major criteria for a definite diagnosis of IE are **positive blood cultures and evidence of endocardial vegetations on either a transthoracic (TTE) or transesophageal echocardiogram (TEE)**. There are also five minor criteria: persistent fever, the risk factors of an invasive procedure within 60 days, a prosthetic valve, current intravenous drug use, and the classic signs of Janeway lesions, Osler's nodes or Roth's spots (vascular and immunologic phenomena). However, many criteria can be missed given the subtle evolution and pathophysiology of RSIE.

The prognosis is mainly determined by the early diagnosis and early medical/surgical management to decrease complications and death.

The aim our study is to report clinical, investigation, management and outcome data in 5 patients diagnosed with RSIE in our department during the last 2 years.

### Methods:-

All the patients data were recorded in a tertiary care university hospital from 2018 to 2020.

The diagnosis of IE was based on modified Dukes criteria. There was no history of IV drug abuse in any of the patients.

Clinical, microbiological, radiographic investigations, management, and follow-up information were analyzed.

### Results:-

#### History and clinical presentation :

All of our patients were young aged females; none of them had cardiac devices or history of drug use. Persistent fever was the most common clinical presentation. Interestingly, 4 patients presented clinical heart failure.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	8	17	21	<b>19</b>	<b>14</b>
Sexe	F	F	F	F	<b>F</b>
History	-	repeated tonsillitis	repeated tonsillitis	Tuberculosis contagion  Hypothyroidism	repeated tonsillitis
Symptoms	Persistent fever  Abdominal pain	Persistent fever  Dyspnea	Persistent fever  Dyspnea	Persistent fever  Profound asthenia  Loss of appetite	Persistent fever  Dyspnea

Clinical examination	-T=39.5 °C, -HR=140/min -3/6 tricuspid holosytolic murmur -lower limb edema, jugular vein distension, hepatomegaly and ascite	-T=38.5 °C, -HR=130/min -5/6 tricuspid holosytolic murmur -lower limb edema, jugular vein distension, hepatomegaly and ascite	-T=39,5 °C, -HR=100/min -5/6 tricuspid holosytolic murmur -lower limb edema, jugular vein distension, hepatomegaly and ascite -Petechial purpura on lower limbs	- T=40 °C, -HR=130/min -5/6 tricuspid holosytolic murmur -5/6 pulmonary holosytolic murmur -lower limb edema, jugular vein distension, hepatomegaly and ascite	- T=37,8 °C, -HR=98/min -3/6 pulmonary holosytolic murmur -Pronouced P2 sound
EKG	sinus tachycardia with no signs of myocardial injury	Sinus tachycardia with right bundle block	Sinus tachycardia	Sinus tachycardia RVH + RAH Right bundle block	Sinus tachycardia RAH
Mode of entry	-	<b>Recent oral care</b>	<b>Poor oral care</b>	<b>Poor oral care</b>	-

**Imaging**

3 patients had isolated tricuspid valve IE, one patient had isolated pulmonary valve IE, and one patient have both tricuspid and pulmonary valve IE.

	Case 1	Case 2	Case 3	Case 4	Case 5
CT radio	cardiomegaly with a cardiothoracic ratio of 0.6	cardiomegaly with a cardiothoracic ratio of 0.78	cardiomegaly with a cardiothoracic ratio of 0.6	cardiomegaly with a cardiothoracic ratio of 0.8	cardiomegaly with a cardiothoracic ratio of 0.65

TTE	Two tricuspid valve vegetations (0,6*0,5, 0,7*0,5 mm) with severe tricuspid regurgitation  Hypoplastic tricuspid septal leaflet	two tricuspid valve mobile vegetations (largest measured 25mm) with severe tricuspid regurgitation with a 8 mm ventricular septum defect	highly mobile vegetation image on the tricuspid valve measuring 28.5 mm,  Mitral and aortic valve leaflets are thick with calcifications which suggest the rheumatic origin of tricuspid valve disease	Magma of vegetation on the tricuspid valve  Magma of vegetations on the pulmonary valve  Pericardial effusion of great abundance  Severe tricuspid regurgitation  Severe pulmonary regurgitation  No evident etiology was found	Pulmonary valve vegetation 15mm*10mm  Atrial septum defect
CT angiogram	-	-	-	<p><b>Multiple AP vegetations</b></p> <p><b>Pulmonary infarction</b></p> <p><b>Pneumatocele</b></p> <p><b>Polyserite</b></p>	-

Tab 2: imaging data of patients

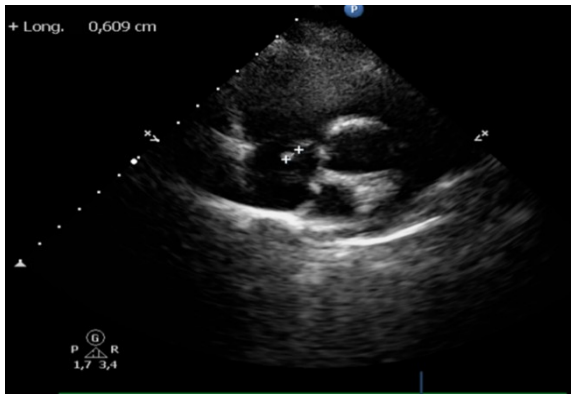


Figure 1: 2 tricuspid valve vegetations (case 1)

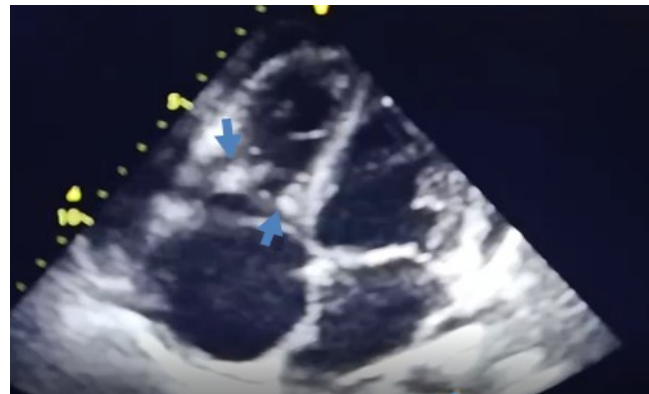


Figure 2: 2 tricuspid valve vegetations (case 2)



Fig 3: TV vegetation measuring 28,5mm with a 20 mm Ventricular septum defect (case 3)

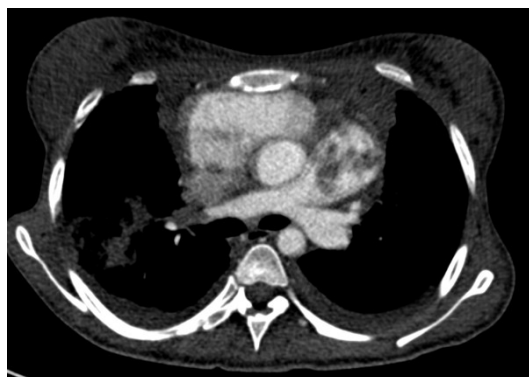


Fig 4: multiple pulmonary vegetations (case 4)



Fig 5: pericardial effusion of great abundance + dilated right atrium

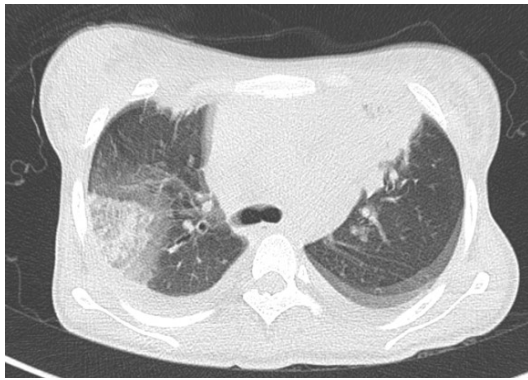


Fig 6: pulmonary infarction (case 4)



Fig 7: pneumatocele (case 4)

□ **Blood culture:**

Blood cultures were negative in two cases, whilst two others were positive to Streptococcus (alpha)

Tab 3: Data of blood culture of our patient

	Case 1	Case 2	Case 3	Case 4	Case 5
Blood culture	Negative	Streptococcus (alpha)	Streptococcus (alpha)	Staphylococcus (alpha)	Negative

□ **Management and follow up :**

Tab 4: Management and follow up of our patients

	Case 1	Case 2	Case 3	Case 4	Case 5
Medical	Ceftriaxone (6weeks) Gentamycin(2 weeks)  Furosemide  Digoxin	Vancomycine (2weeks)  Furosemide	Ceftriaxone (2 weeks)  Furosemide	(2 weeks)	Ceftriaxone (6weeks) Gentamycin(2 weeks)  Furosemide
Surgical	Tricuspid valve replacement with a biological prosthetic valve	Tricuspid valve replacement with a biological prosthetic valve  Closure of the VSD with a pericardial patch	Tricuspid valve replacement with a biological prosthetic valve	-	Pulmonary valve replacement with a biological prosthetic valve  DEVEGA tricuspid plasty  Closure of ASD



Follow up	Discharged after 1 week of surgery	Discharged after 1 week of surgery	Excellent after 7 months	Death after 1 week	Discharged after 2 week of surgery
	Doing well after 6 months of follow up	Doing well after 1 year of follow up		Cause of death: massive pulmonary embolism	Doing well after 6 months of follow up

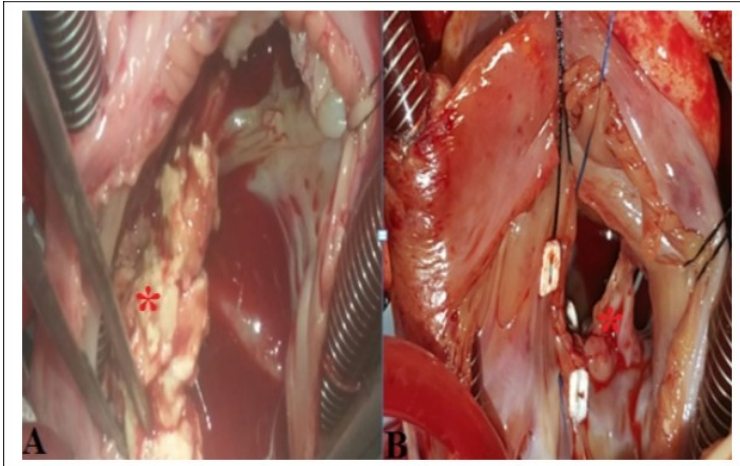


Fig 9: Tricuspid valve replacement with biological prosthesis

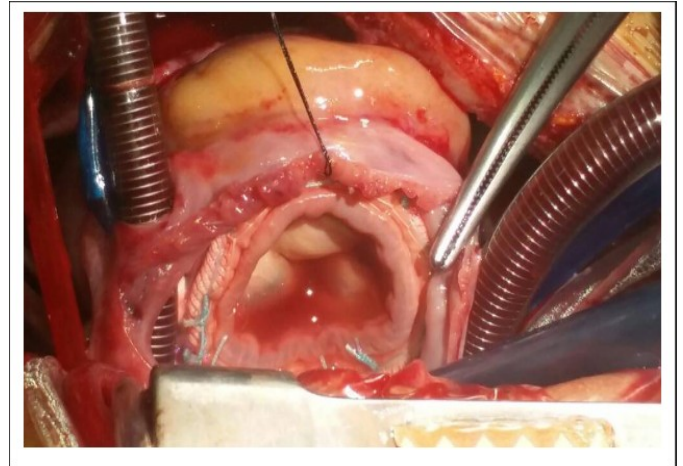


Fig 8 : Surgical view of perforated tricuspid leaflet

### Discussion:-

Incidence of RSIE has been described as 5%–10% of IE. However, recently published studies indicate an increased incidence of 10%–20% (4–6). It is often associated with intravenous drug use (IVDU), intracardiac devices, and central venous catheters, all of which have become more prevalent in the western world over the past 20 years (1)

### Primary prevention

In our context, very few studies have estimated the prevalence of RSIE; However, rheumatic heart disease remains the most prevalent etiology as the prevalence of this pathology is high in Africa (7–9).

Moreover, IE is also well-recognized complication of ventricular septal defects with an incidence in several large series of approximately 1/1000 patient years. VSD, aortic stenosis, coarctation of the aorta, and patent ductus arteriosus are associated with high-velocity or turbulent flows, and are at a much higher risk for developing infective endocarditis. Conversely, defects such as secundum atrial septal defects are not associated with infective endocarditis. The infective process may involve the margins of the defect or the aortic or tricuspid valve, the principal causative organisms being streptococcus viridans and staphylococcus aureus (10) .

In our case series, one patient had a VSD and another one had an ASD, no evident mode of entry was founded in the two others except recent oral care and poor oral hygiene. Currently, the American Heart Association/American College of Cardiology and the task force of the European Society of Cardiology for IE antibiotic prophylaxis have precluded the need for antibiotics in patients with acyanotic congenital hemodynamically insignificant atrial and ventricular septal defects (11).

As rheumatic heart disease is a major public health problem in our country, it can be interesting to evaluate the interest of antibiotic prophylaxis in patients with VSDs and ASDs; larger studies in our context (North Africa) need to be carried out.

### Feature of valvular involvement

Another interesting observation in our case series is the existence of isolated pulmonary valve IE in one patient, and the coexistence of pulmonary and tricuspid valve IE in another one. In literature review, isolated pulmonary valve endocarditis is rare. It is assumed that its rarity is due to the low pressure gradients within the right heart, the low prevalence of congenital malformations, the lower oxygen content of venous blood, and the differences in the covering and vascularization of the right heart endothelium (12). Most cases of pulmonary valve endocarditis in children are secondary to the presence of a congenitally abnormal pulmonary valve and in adults secondary to intravenous drug abuse. Isolated pulmonary valve endocarditis has also been identified in patients undergoing chronic hemodialysis and orthotopic liver transplantation (13,14). A significant number of patients present with primarily pulmonary symptoms such as pleuritic chest pain, cough, and dyspnea. When peripheral embolic or neurologic features occur, either left-sided endocarditis or paradoxical embolism should be considered.

The clinical presentation of isolated pulmonary valve endocarditis in one patient included persistent fever, and in the other one features of multiple septic pulmonary embolism, and a new pulmonary murmur. A review of the published data indicated that the role of surgery in isolated pulmonary valve endocarditis is unclear. Recurrent pulmonary emboli are not an indication for surgery, which is only needed if fever persists despite 3 weeks of appropriate antibiotic treatment in the absence of a pulmonary abscess (15). Surgical options include debridement of the infected area, vegetation excision with either valve preservation or valve repair or valve replacement. Preservation of the native pulmonary valve is recommended whenever possible, and use of a homograft or xenograft is preferred if replacement is unavoidable, which was performed in our patient with isolated pulmonary IE.

### Micro-organisms and antibiotic therapy features:

The typical microorganisms causing right sided IE are listed in Table 5. *Staphylococcus aureus* is the predominant organism (60–90% of cases) in rightsided IE, with a steadily increasing proportion of methicillin resistant *Staphylococcus aureus* strains and polymicrobial infections (1). Streptococcal and coagulase negative staphylococcal infections are also frequent causes of right sided IE, with *S. pneumoniae* IE occurring more commonly in the setting of chronic alcoholism, regardless of IVDU. However, *S. pneumoniae* is still more likely to involve the left side of the heart, with right sided IE accounting for <10% of cases (1). In our context, streptococcus is most likely to be the causative bacterial agent incriminated in RSIE.

Organism	Features
<i>Staphylococcus aureus</i>	Most prevalent pathogen (60–90% of cases), increase in methicillin-resistant <i>Staphylococcus aureus</i> predominantly in intravenous drug use
Coagulase-negative <i>Staphylococcus</i>	Risk factors: alcoholism, prosthetic valves, vascular catheters
Streptococci (especially <i>S. pneumoniae</i> )	Prevalent in alcoholics, still more dominant in left-sided infective endocarditis
<i>Pseudomonas aeruginosa</i> and other gram-negative bacteria	Increasing prevalence
Fungi	Relatively high mortality, incidence rising due to immunocompromised, aging population and intracardiac devices

Tab 5: Common causative micro-organisms in RSIE



Intravenous antibiotics are the cornerstone of treatment for right-sided IE affecting the TV. However, surgical intervention may be warranted in several situations, as described in *Table 6*. (1). The proportion of patients who are reported to undergo surgery for right-sided IE ranges from 5% to 40% (16). Surgical techniques consist of vegetation removal, radical debridement of vegetations, and infected tissue and valve repair. The use of prosthetic material (ie, valve replacement) should be avoided when possible (17). Surgical techniques can be also divided into “prosthetic” (tricuspid valve replacement or ring annuloplasty) or “nonprosthetic” (annuloplasty, bicuspidization, vegetomy [solely removing the vegetation], or valvectomy [removal of tricuspid valve leaflet]). For right-sided IE associated with IVDU, surgical management should strive to avoid artificial material and focus on vegetation removal and valve repair, which are associated with better late survival (17). In our case series, 4 patients underwent surgical treatment; the indications were the presence of right heart failure secondary to severe tricuspid regurgitation and the size of the vegetations. Unfortunately, one patient died of massive pulmonary embolism despite well conducted antibiotherapy.

Microorganisms difficult to eradicate (eg, persistent fungi)	Persistent bacteremia for >7 d (eg, <i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> ) despite adequate antimicrobial therapy
Large, persistent tricuspid valve vegetations (>20 mm)	Recurrent pulmonary emboli with or without concomitant right heart failure
Right heart failure secondary to severe tricuspid regurgitation	Abscess (more common in the setting of prosthetic valve)

Tab 6: Indications for Surgical Interventions for Right-Sided Infective Endocarditis.

The most common complications include valvular insufficiency, abscess formation, and septic pulmonary embolism (18). In a recent review, a mean of 1.6 complications per right-sided IE patient were reported, and the most common complications were valvular insufficiency, embolic events, and abscess formation (19). Pulmonary involvement occurred in 80% of these cases and varied from minor atelectasis to large infiltrates, pleural exudates, and cavitation, generally involving the lower lobes.

Invasive disease, such as the formation of cardiac abscesses, cavities, or pseudo-aneurysms, is rare in right-sided IE (0.7%) and the infection is usually limited to the TV leaflets and does not extend beyond the annulus. In contrast, invasive IE is significantly more common in aortic valve IE (65%) and mitral valve IE (31%). It has been hypothesized that the development of cardiac abscesses, cavities, or pseudoaneurysms requires high intracavitary pressures and thus almost never occur in the low pressure right-sided chambers (20).

### Conclusion:-

RSIE is rare and occurs in a wide range of underlying conditions like implantable electronic devices, indwelling catheters, CHD and immunocompromised state. Surprisingly, it can occur in young individuals without known risk factors. In our context, rheumatic heart disease remains the most incriminated etiology which lead us to question three essential points:

1. The interest of antibiotic prophylaxis in young patients with VSDs
2. The use of empiric antibiotics with action against streptococcus

3. Early surgical treatment in case of symptomatic severe valve dysfunction, and large vegetations.

### Conflict of Interests

There are no conflicts of interests for the development of this publication.

### Ethical Standards

Informed consent was obtained from the patient parents for the publication of this case.

### References:-

1. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta J-P, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 21 nov 2015;36(44):3075-128. DOI: [10.1093/eurheartj/ehv319](https://doi.org/10.1093/eurheartj/ehv319)
2. United States Department Of Health And Human Services. Substance Abuse And Mental Health Services Administration. Center For Behavioral Health Statistics And Quality. National Survey on Drug Use and Health, 2013: Version 3 [Internet]. ICPSR - Interuniversity Consortium for Political and Social Research; 2014 [cit  29 sept 2020]. DOI: [10.3886/ICPSR35509.V3](https://doi.org/10.3886/ICPSR35509.V3)
3. Akinosoglou K, Apostolakis E, Marangos M, Pasvol G. Native valve right sided infective endocarditis. *Eur J Intern Med*. sept 2013;24(6):510-9. DOI: [10.1016/j.ejim.2013.01.010](https://doi.org/10.1016/j.ejim.2013.01.010)
4. Stavi V, Brandstaetter E, Sagy I, Sapunar S, Nevzorov R, Bartal C, et al. Comparison of Clinical Characteristics and Prognosis in Patients with Right- and Left-sided Infective Endocarditis. *Rambam Maimonides Med J*. 28 janv 2019;10(1):e0003. DOI: [10.5041/RMMJ.10338](https://doi.org/10.5041/RMMJ.10338)
5. Ortiz C, L pez J, Garcia H, Sevilla T, Revilla A, Vilacosta I, et al. Clinical Classification and Prognosis of Isolated Right-Sided Infective Endocarditis. *Medicine (Baltimore)* [Internet]. 12 d c 2014 [cit  29 sept 2020];93(27). DOI: [10.1097/MD.0000000000000137](https://doi.org/10.1097/MD.0000000000000137)
6. Galal H, Rifaei O, Abdel Rahman M, El-Sayed H. Prevalence and characteristics of tricuspid valve endocarditis among patients presented to Ain Shams Hospital echocardiography lab; one year study. *The Egyptian Heart Journal*. juin 2018;70(2):59-63. DOI: [10.1016/j.ehj.2017.12.009](https://doi.org/10.1016/j.ehj.2017.12.009)
7. Otto H, Saether SG, Banteyrga L, Haugen BO, Skjaerpe T. High prevalence of subclinical rheumatic heart disease in pregnant women in a developing country: an echocardiographic study. *Echocardiography*. nov 2011;28(10):1049-53. DOI: [10.1111/j.1540-8175.2011.01520.x](https://doi.org/10.1111/j.1540-8175.2011.01520.x)
8. Z hlke LJ, Engel ME, Watkins D, Mayosi BM. Incidence, prevalence and outcome of rheumatic heart disease in South Africa: a systematic review of contemporary studies. *Int J Cardiol*. 15 nov 2015;199:375-83. DOI: [10.1016/j.ijcard.2015.06.145](https://doi.org/10.1016/j.ijcard.2015.06.145)
9. Beaton A, Okello E, Lwabi P, Mondo C, McCarter R, Sable C. Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren. *Circulation*. 26 juin 2012;125(25):3127-32. DOI: [10.1161/CIRCULATIONAHA.112.092312](https://doi.org/10.1161/CIRCULATIONAHA.112.092312)
10. Neumayer U, Stone S, Somerville J. Small ventricular septal defects in adults. *Eur Heart J*. oct 1998;19(10):1573-82. DOI: [10.1053/ehj.1998.1083](https://doi.org/10.1053/ehj.1998.1083)
11. Pant S, Patel NJ, Deshmukh A, Golwala H, Patel N, Badheka A, et al. Trends in infective endocarditis incidence, microbiology, and valve replacement in the United States from 2000 to 2011. *J Am Coll Cardiol*. 19 mai 2015;65(19):2070-6. DOI: [10.1016/j.jacc.2015.03.518](https://doi.org/10.1016/j.jacc.2015.03.518)
12. Ramadan FB, Beanlands DS, Burwash IG. Isolated pulmonic valve endocarditis in healthy hearts: a case report and review of the literature. *Can J Cardiol*. oct 2000;16(10):1282-8. PMID: [11064303](https://pubmed.ncbi.nlm.nih.gov/11064303/)
13. Kamaraju S, Nelson K, Williams DN, Ayenew W, Modi KS. *Staphylococcus lugdunensis* pulmonary valve endocarditis in a patient on chronic hemodialysis. *Am J Nephrol*. 1999;19(5):605-8. DOI: [10.1159/000013528](https://doi.org/10.1159/000013528)
14. Hearn CJ, Smedira NG. Pulmonic valve endocarditis after orthotopic liver transplantation. *Liver Transpl Surg*. sept 1999;5(5):456-7. DOI: [10.1002/lt.500050509](https://doi.org/10.1002/lt.500050509)
15. Petterson G, Carbon C. Recommendations for the surgical treatment of endocarditis. *Clin Microbiol Infect*. 1998;4 Suppl 3:S34-46. PMID: [11869261](https://pubmed.ncbi.nlm.nih.gov/11869261/)
16. Weber C, Gassa A, Eghbalzadeh K, Merkle J, Djordjevic I, Maier J, et al. Characteristics and outcomes of patients with right-sided endocarditis undergoing cardiac surgery. *Annals of Cardiothoracic Surgery*. 16 ao t 2019;8(6):645-653-653. DOI: [10.3978/16646](https://doi.org/10.3978/16646)

17. Akinosoglou K, Apostolakis E, Koutsogiannis N, Leivaditis V, Gogos CA. Right-sided infective endocarditis: surgical management. *Eur J Cardiothorac Surg.* sept 2012;42(3):470-9. [DOI: 10.1093/ejcts/ezs084](https://doi.org/10.1093/ejcts/ezs084)
18. Galili Y, Lytle M, Carlan S, Madruga M. Bilateral Pneumothoraces: A Rare Complication of Septic Pulmonary Emboli in Intravenous Drug Abusers. *Am J Case Rep.* 14 juill 2018;19:829-32. [DOI: 10.12659/AJCR.910371](https://doi.org/10.12659/AJCR.910371)
19. Yuan S-M. Right-sided infective endocarditis: recent epidemiologic changes. *Int J Clin Exp Med.* 2014;7(1):199-218. [PMID: 24482708](https://pubmed.ncbi.nlm.nih.gov/24482708/)
20. Hussain ST, Shrestha NK, Witten J, Gordon SM, Houghtaling PL, Tingleff J, et al. Rarity of invasiveness in right-sided infective endocarditis. *J Thorac Cardiovasc Surg.* 2018;155(1):54-61.e1. [DOI: 10.1016/j.jtcvs.2017.07.068](https://doi.org/10.1016/j.jtcvs.2017.07.068).