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Prof Paolo G Camici

Editor in Chief

International Journal of Cardiology

London 19/09/2017

Dear Professor Camici,

Please find enclosed the Editorial you requested related to the article entitle "Incidence, Predictors and Outcomes of Infective Endocarditis in a Contemporary Adult Congenital Heart Disease Population".

In this Editorial we have attempted to highlight the importance for all healthcare providers to be vigilant and adequately prepared to recognise symptoms of infective endocarditis in patients with congenital heart disease, as it is likely to reduce the related morbidity. We have also stressed the importance of referring this particular group of patients to a specialised centre where a well-established "Endocarditis Team" can ensure the most appropriate clinical management.

Best wishes,

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Infective Endocarditis in Patients with Congenital Heart Disease: When, Where and How.

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Ubi pus, ibi evacua (where there is pus, there evacuate it) is a Latin aphorism attributed to the Greek Galen of Pergamon and considered to be the only remedy for infections in the second century AD. The introduction of antibiotics has radically changed the treatment of infections, but surgery still plays an important role in the management of infective endocarditis (IE), particularly in the context of congenital heart disease (CHD). In this edition of the *IJC* Moore et al.ⁱ, and other contemporary reports, suggest that the incidence of IE amongst adults with CHD remains substantial, between 0.9ⁱ and 1.3ⁱⁱ cases/1,000 patient-years, as opposed to the non-CHD population (5-7/100,000 patient-year)ⁱⁱⁱ. Our group^{iv} also reported a 20% recurrence rate in adults with CHD. Mortality related to IE also remains significant and varies between reports (4-16%)^{i,iii}.

It is, thus, important to identify CHD patients who are at increased risk of developing IE and its complications. While patients with complex CHD are at higher risk of IE, the incidence of IE in simple lesions appears also notable. Moore et al.ⁱ report that IE was most common in complex CHD and ventricular septal defects (VSDs). There was a predominance of left sided infections, and prosthetic material was involved in approximately 50% of cases, even though other authorsⁱⁱ have demonstrated that the risk is lower for non-valvar prosthetic material (including valve repair) after 6 months from implantation. These observations are reflected in the most recent International Guidelinesⁱⁱⁱ, which recommend antibiotic prophylaxis in patients with previous IE, as well as those with prosthetic valves, or recently implanted or non-endothelialised prosthesis and cyanotic lesions. While not fulfilling the criteria for prophylaxis, patients with simple lesions, especially VSDs and bicuspid aortic valves (BAVs), should be monitored closely and investigated with similar urgency when presenting with symptoms suspicious of IE.

Moore et al.ⁱ also report a high mortality related to IE, higher than previous reports. Major contributors to death were multiorgan failure and systemic emboli, especially strokes. Remarkably, most of the deaths occurred in patients with simple lesions (BAV and VSD) with or without prior surgery. There is urgent need for models that can better predict the risk of developing IE and its complications in individual patients. One such model is proposed by Kuijpers et al.ⁱⁱ, developed and validated on 14,224 CHD patients, which appears to provide accurate predictions of the risk of IE for up to 10 years of follow-up. Mortality from IE is likely to be lowered by improving the time from the onset of symptoms to definitive diagnosis. Unfortunately, a long delay between symptoms and referral to a tertiary centre is not uncommon, even nowadays, with Moore et al. reporting an average time between symptom onset and diagnosis of 27 days.

While the modified Duke criteria^v apply to all patients with suspected IE, there are special considerations that are particularly relevant to CHD patients. The identification of the organism responsible is of vital importance in all patients, especially those with prosthetic material. When the clinical suspicion is high, novel techniques for identifying the culprit microorganism (e.g. PCR amplification) should be considered. Novel atypical and iatrogenic pathogens, such as the recently identified *Mycobacterium Chimaera* transmitted during cardiopulmonary bypass, should be suspected and investigated for^{vi}. Transthoracic echocardiography is often inconclusive and a transoesophageal echo is required in 40^{iv}-69%ⁱ of CHD cases. Infected sites at distal structures can still be missed (e.g. stents or other prosthetic material within branch pulmonary arteries), while the interpretation of suspicious findings on old pacing wires or within older conduits can be arduous. Advanced techniques, such as ¹⁸F-FDG-PET/CT angiography, can increase the diagnostic accuracy^{vii} of the Duke criteria and support the management of IE in CHD.

Recent guidelinesⁱⁱⁱ have underlined the importance of establishing well-defined "Endocarditis Teams" within tertiary centres that guarantees high levels of expertise from practitioners in several specialties. As IE is significant more common in CHD compared to non-CHD patients, major specialist CHD centres have long developed such a multidisciplinary approach to IE, with cardiologists, microbiologists, surgeons, and specialists in infectious disease and other disciplines working closely to ensure optimal outcomes. All CHD patients with IE should, thus, be managed in CHD centres, especially as, in our experience, surgical intervention during the same admission is required in over a third of cases^{iv} and has to be performed by a surgeon trained in CHD.

As the characteristics of the adult CHD population constantly change with the introduction of novel surgical and interventional techniques (Figure1), so does the risk profile of patients who may develop IE. Hence, risk scores need to be reviewed frequently and advanced technologies are likely to become increasingly important in establishing the diagnosis in a timely fashion. Particular emphasis should be placed on education, raising patient awareness of this condition^{viii} and stressing the importance of maintaining good dental and skin hygiene and promptly reporting symptoms suggestive of IE. Finally, education of all medical practitioners involved in the care of CHD patients on the importance of early diagnosis and the need for a high index of suspicion, should achieve more timely referral of IE cases to tertiary centres.



Figure1: Infected percutaneous valve removed from the pulmonary position in a patient with Tetralogy of Fallot.

ⁱ B Moore, J Cao, I Kotchetkova, D Celermajer Incidence, Predictors and Outcomes of Infective Endocarditis in a Contemporary Adult Congenital Heart Disease Population Int J Cardiol. 2017

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ⁱⁱⁱ Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, Dulgheru R, El Khoury G, Erba PA, Iung B, Miro JM, Mulder BJ, Plonska-Gosciniak E, Price S, Roos-Hesselink J, Snygg-Martin U, Thuny F, Tornos Mas P, Vilacosta I, Zamorano JL; 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).

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^v Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis 2000;30:633-8.

^{vi} Kohler P, Kuster SP, Bloemberg G, Schulthess B, Frank M, Tanner FC, et al. Healthcare-associated prosthetic heart valve, aortic vascular graft, and disseminated *Mycobacterium chimaera* infections subsequent to open heart surgery. [Eur Heart J](#). 2015;36:2745–53. 10.1093/eurheartj/ehv342

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The authors report no relationships that could be construed as a conflict of interest.

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. *Int. J. Cardiol.* 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

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