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Importance of Dermatology in Infective Endocarditis

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1. Introduction

Infective endocarditis (IE) is a rare affection with an annual incidence of between 15 to 60 cases per million. If untreated, IE is fatal, and the overall mortality is evaluated above 20%. IE is an endovascular microbial infection of intracardiac structures. The early characteristic lesion corresponds to variable sized vegetation leading to valvular destruction and abscess formation.

Epidemiologic profile evolved progressively with decreasing proportion of IE on abnormal native valve compensated by an increased proportion of prosthetic valve IE and native valve IE with previously unrecognized predisposing conditions. Among causative microorganisms, the responsibility of staphylococci is more frequently observed. Diagnosing IE remains a clinical challenge because evolution is insidious and symptoms are polymorphous. This diagnosis must be systematically considered in the presence of purpura, distal necrosis but also in patients who had have chronic dermatosis which correspond to an underestimated potential source of IE.

2. Pathophysiology

Secondary to damage of endothelium, extracellular matrix proteins are exposed leading to development of non-bacterial thrombotic endocarditis (NBTE) with fibrin and platelets. Endothelial damage can occur after mechanical lesions (devices, repeated intravenous injection of particulate material), turbulent blood flow (congenital heart disease, prosthetic valves…), inflammation (chronic rheumatic fever) or degenerative lesions (European society of cardiology [ESC], 2009). NBTE facilitates micro-organism adherence and infection of endothelium (Figure 1).

International specialists (American Heart Association [AHA], 2007; ESC, 2009) no longer differentiate acute, subacute and chronic IE based on usual progression of untreated disease. Indeed, although clinical manifestations are more insidious in subacute IE, severe

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complications can occur and it is currently difficult to determine the onset of the disease. Presently, IE are classified depending on the type of valve damage (right/left-sided, native/prosthetic valve).

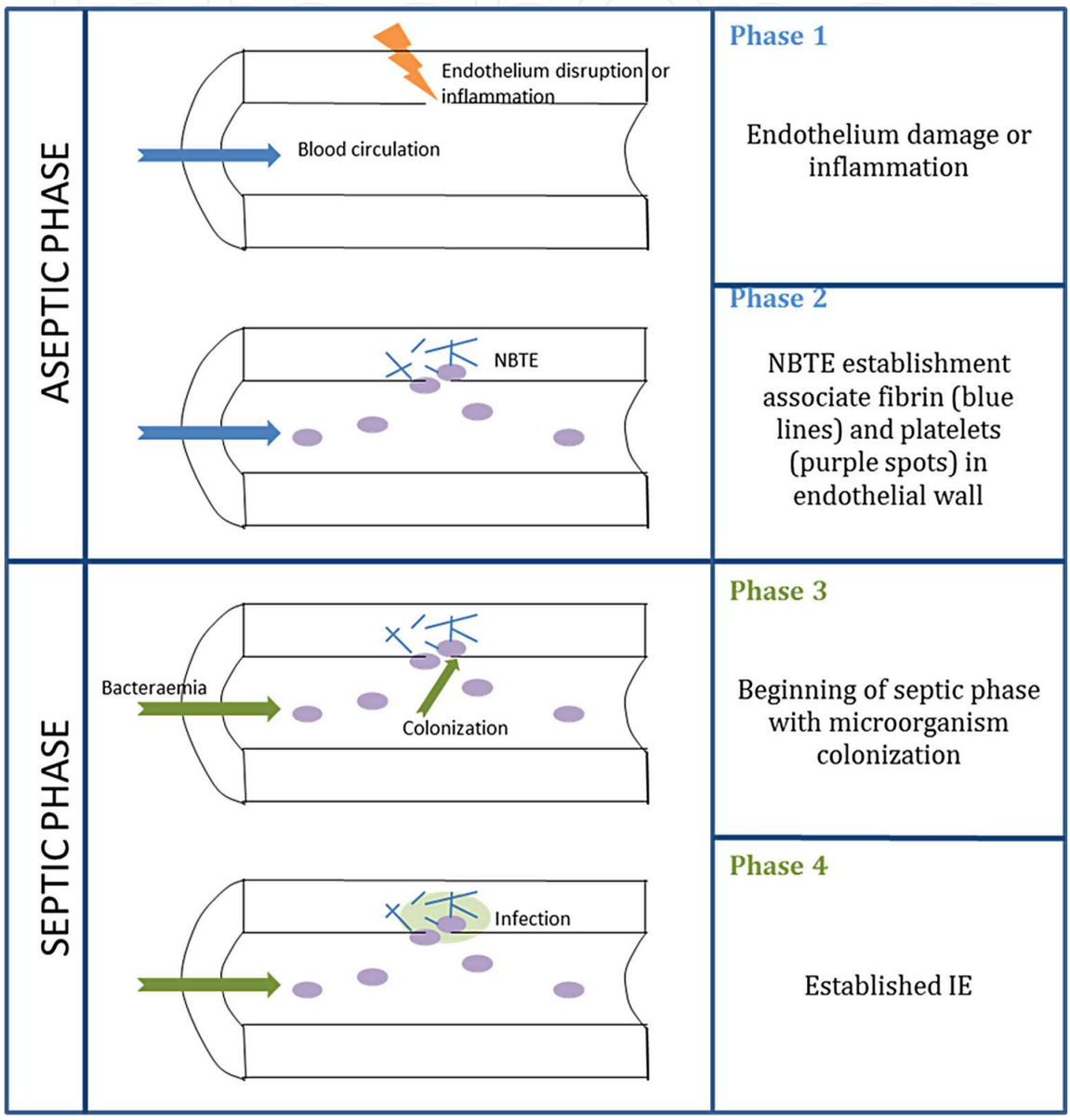

Fig. 1. Pathophysiology of IE with aseptic and septic phases (A. Servy; August 2011). NBTE: non- bacterial thrombotic endocarditis

3. Epidemiology

3.1 Incidence

IE is a rare disease with 2 to 6 per 100 000 persons affected per year (Que, 2011). Classically described in young patients after chronic rheumatic heart disease. Its incidence in industrialized countries is more elevated in at-risk groups, mainly persons older than 65 years old (15 per 100 000 per year). At present, the average is 57 years old (Que, 2011; ESC, 2009).

Native valve IE is the most frequent. Left-sided native valve IE represents 70% of disease incidence and the mortality is evaluated at 15% (25-45% with healthcare-associated). 5-10% of IE affect right-sided native valve, mainly in intravenous-drug users, and patients with congenital heart disease or devices. *Staphylococcus spp* is most frequently involved in right-sided native valve IE and mortality is less than 10% (Que, 2011).

Prosthetic valve IE is also increasing (10-30% of IE), mechanical and bioprosthetic equally. The prevalence of valve prostheses IE is above 6% (0.3-1.2% per year). Left-sided prosthetic valve endocarditis (20% of IE) is the most severe with 20 to 40% mortality. The main germs involved in early prosthetic valve IE (less than one year after cardiac surgery) include staphylococci, fungi and Gram-negative bacilli, whereas late IE is associated with staphylococci, oral streptococci, *S. bovis* and enteroccoci (ESC, 2009).

3.2 Risk factors

3.2.1 Characteristics of patient

The main risk factor is age (median age above 60) (Murdoch, 2009) due to degenerative valve, immunosuppressive conditions and multiple comorbidities. However, edentate people have a lower risk of IE. Digestive portal of entry is frequent in this population, mainly in *S. bovis* and enterococcus IE and should be researched.

Many comorbidities increase the risk of IE, leading to heart diseases. At present, in industrialized countries, chronic rheumatic heart disease has become exceptional and the proportion of degenerative valve lesion and congenital heart disease is more important as well as their responsibility for IE (Moreillon, 2004). Chronic immunosuppressive therapy (chemotherapy, topical corticosteroid…) or affections are predisposing conditions, mainly diabetes mellitus (16% of IE), hemodialysis (8%), cancer (8%) and HIV infection (2%) (Murdoch, 2009). Physicians should be aware of the risk of EI in cases of acute or chronic dermatosis. Chronic bacteria carriers, wounds, and percutaneous invasive procedure increase significantly the risk of bacteremia.

3.2.2 Situations at risk

All iatrogenic invasive procedures are at risk of bacteremia such as catheter, urinary surgery, and endoscopy (Table 1). Nevertheless, intravenous drug users are more at risk (10% of IE) due to poor hygiene. Indeed 55% of active heroin, cocaine and methamphetamine injection drug users report a lifetime history of skin infection mainly in cases of intramuscular injection or frequent heroin or speedball injection (Phillips, 2010). In these cases, *S. aureus* and fungi must be suspected and treated. Dental treatments are too

easily suspected (AHA, 2007; Strom, 1998) whereas most of the time, no procedure or situation at risk are identified and daily bacteremia is often involved (AHA, 2007). In a recent French study (Association pour l'Etude et la Prévention de l'Endocardite Infectieuse [AEPEI], 2002), 63% of IE cases had no situation at risk identified.

<table>
<tr><th colspan="3">Risk factors of IE</th></tr>
<tr><th colspan="2">Patient characteristics</th><th>Situations at risk</th></tr>
<tr><td>Age</td><td rowspan="2">Heart disease and prosthetic valve
Diabetes mellitus
Chronic renal failure
Immunosuppressive affection</td><td rowspan="3">Invasive procedures:
- percutaneous (drug, catheter…) or
- dental
Daily bacteremia
- Brushing teeth
- Chewing …</td></tr>
<tr><td>Comorbidities</td></tr>
<tr><td>Treatment</td><td>Immunosuppressive therapy</td></tr>
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Table 1. Procedures and situations at risk of bacteremia.

3.3 Causal microorganisms

Distribution of causative microorganisms of IE is different, depending on the patient's characteristics (Table 2) and portal of entry. Gram-positive bacteria are the most frequent microorganisms. They are responsible for more than 80% of IE because they have greatest ability to adhere and colonize damaged valves (Que, 2011).

Microorganisms (%)	Valve affected			
	Native valve IE		Intracardiac device IE	
	Drug abusers	Others patients	Prosthetic valve	Others
Staphylococcus aureus	68	28	23	35
Coagulase-negative staphylococcus	3	9	17	26
Viridans group streptococci	10	21	12	8
Streptococcus bovis	1	7	5	3
Enterococcus ssp	5	11	12	6
HACEK	0	2	2	1
Fungi	1	1	4	1
Polymicromial	3	1	0.8	0
Negative culture findings	5	9	12	11

Table 2. Microbiologic etiology of IE depend on patient's characteristics (Murdoch, 2009). HACEK: Haemophilus (parainfluenzae, aphrophilus, paraphrophilus and influenza), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella (kingae and dentrificans).

Although increasing involvement of oral streptococci, streptococcaceae remain the main pathogen (nearly 60% of IE). In streptococci group, group D (*S. bovis*…) are found in 25%, oral streptococci in 17% and pyogenic streptococci (*S. agalactiae, S. pyogenes*) in 6% of IE.

Enterococci (mainly *E. faecalis*) are also frequent (8%), mainly in elderly people and prosthetic valve carriers (AEPEI, 2002). Urinary and digestive portal of entry (including colon cancer, and diverticulitis) must be researched with colonoscopy and imaging. Presence of *S. bovis* equally implies digestive portal of entry.

The role of Staphylococcaceae is increasing (20-34% of IE) with 23% of IE due to *S. aureus* and 6% to coagulase-negative staphylococci (AEPEI, 2002; Miro, 2005). Staphylococcus IE is more frequent in intravenous drug users, HIV patients, right-sided IE and iatrogenic infection. The prevalence of IE in patients with *Staphylococcus aureus* bacteremia is elevated (22%) and some authors recommend a systematic echocardiography in this situation (Rasmussen, 2011).

The responsibility of others germs is lesser and unusually several microorganisms are associated in rare instances (less than 5%). No germ is identified in 5% of cases (AEPEI, 2002).

3.4 Portals of entry

Any site of infection can be responsible of IE. However, some portals of entry are more frequent and must be investigated. Cutaneous portal of entry is frequent (20%) and often misdiagnosed by physicians. In these cases, IE mainly developed on traumatic or chronic wounds, infected or inflammatory dermatosis, intravenous drug use, percutaneous iatrogenic procedures… Dental portal of entry is observed in 9% of cases (poor dental condition, dental procedure). Genitourinary and digestive portal of entry are observed respectively in above 2-11% and 5-9% (AEPEI, 2002; Tornos, 2005).

4. Diagnosis

4.1 Clinical manifestations

Clinical diagnosis of IE is often difficult because of various clinical manifestations and insidious evolution. Moreover, atypical presentation is usual in elderly, immunocompromised patients (lack of fever) and carriers of prosthetic valve, mainly in earlier phase (less than one 1 year after surgery). In fact, in this last group, blood cultures are frequently negative, echocardiography is difficult (ESC, 2009) and inflammatory syndrome and fever is classical even in absence of IE. So, clinical suspicion of IE should be systematically discussed in these cases, and complementary investigations performed.

4.1.1 General signs

Fever is the most frequent sign (approximately 90%) and usually temperature normalizes within 1 week (5-10 days) under adaptive antibiotherapy. An impaired general health condition can be observed with weight loss, fatigue and anorexia.

4.1.2 Cardiological signs

Cardiological manifestations are nearly constant. Heart murmurs are found in up 85% of IE (ESC, 2009) but occurrence of new ones (48%) or increasing of an older murmur (20%) are more evocative (Murdoch, 2009). Clinical manifestations of heart complications can be added (mainly heart failure).

4.1.3 Extracardiac manifestations

Extracardiac manifestations are also frequent, particularly in right-sided IE (78% versus 52% in left-sided IE) with 68% of pulmonary embolism (AEPEI, 2002).

If IE is suspected, dermatological manifestations should be systematically searched and discussed despite rarity (5 to 25% of IE present skin manifestations) not only for diagnosis but also for prognostic (Table 5). They can easily lead to suspicion of IE. In our recent study (unpublished data), we demonstrated a link between the presence of cutaneous signs and embolic events (18.4% of embolic events in lack of cutaneous sign versus 33%) without higher mortality. Dermatological manifestations (Figures 2 and 3) seem to be also less frequently observed with enteroccoci infection (14.5% versus 27.1%) (Martínez-Marcos, 2009).

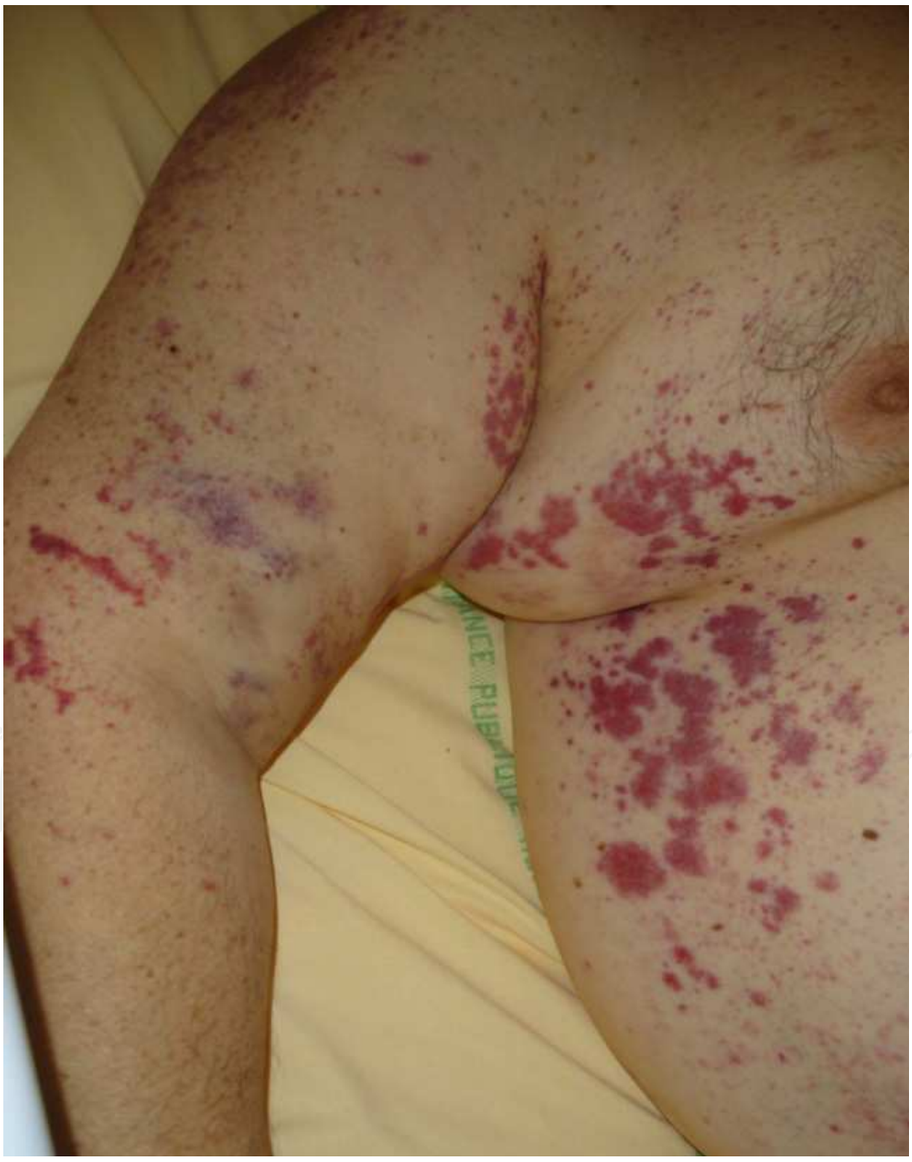

Fig. 2. Vascular purpura on trunk and arms during IE.

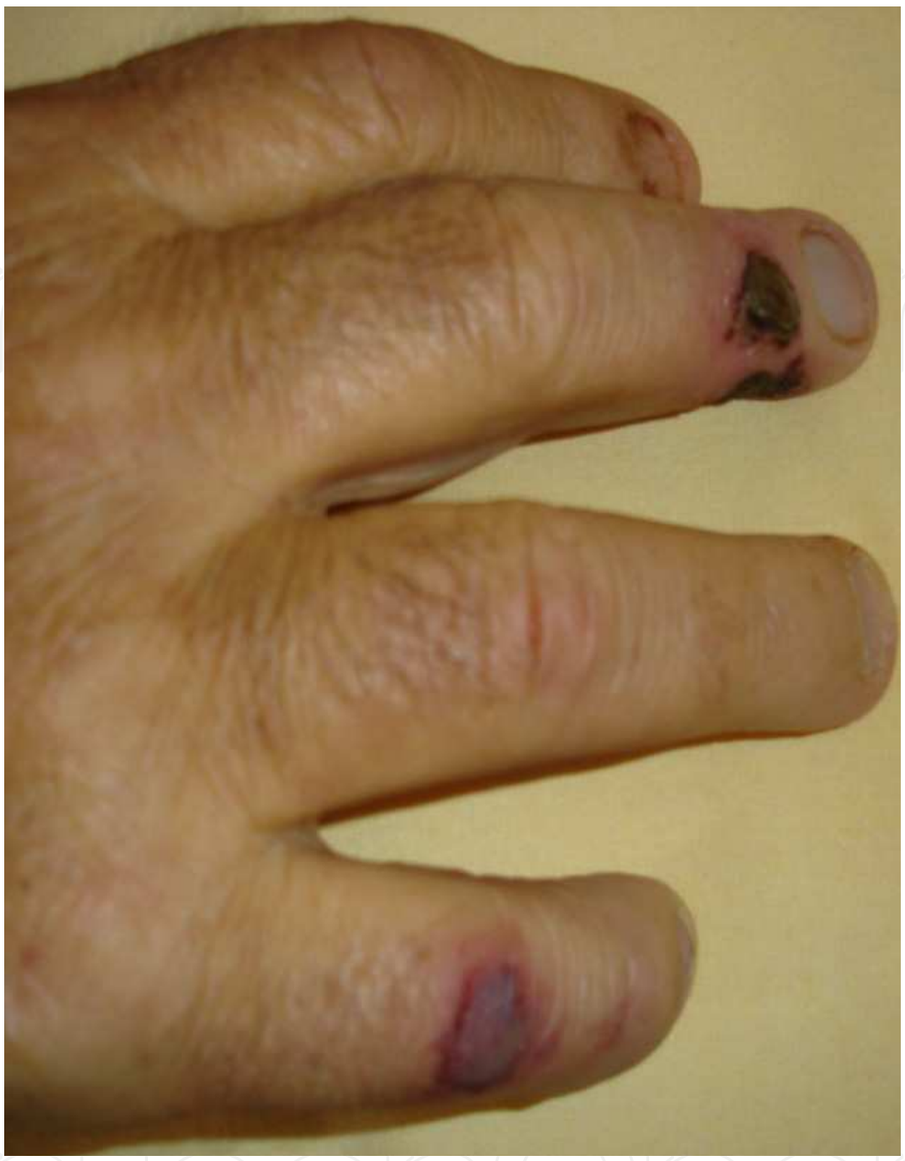

Fig. 3. Necrotic lesions of fingers (same patient): old Janeway lesion or purpura lesion.

- **Osler's lesions** are specific and described as purple painful nodes on palms, soles, fingertips, pulp of the toes or sometimes on ears (Farrior, 1976). Unfortunately, prevalence is low (3-3.6%) (AEPEI, 2002; Murdoch, 2009) and lesions disappear in a few days without sequelae. In a study including 43 intravenous-drug users IE, Osler's nodes were observed in 50% of left-sided IE whereas none were noticed in right-sided IE (33 right-sided). Moreover, bacteriological study of nodes revealed the same microorganisms as in blood (*S. aureus*).
- **Janeway lesions** are small non tender erythematous and painless macular (sometimes nodular!) localized on palms or soles (2-5% of IE) (AEPEI, 2002; Murdoch, 2009). These lesions are equally specific and their differenciation difference with Osler nodes is often as difficult, clinically as histologically.

- **Purpura** is more frequent (7.3%) (AEPEI, 2002) but not specific. Its pathophysiology is still unclear including often septic embolism and/or leucocytoclastic cutaneous vasculitis by complex immune depositions (Lévesque 1999). Vascular purpura is characterized by red lesions that don't blanch on applying pressure, caused by erythrocyte extravasation. Lesions are localized on lower parts of the body (legs, back). In IE, lesions are also described on the neck and near the clavicles. IE mucosal purpura is often observed on conjunctivae and mouth (Heffner, 1979).
- **Splinter haemorrhages** are common in many diseases and found in 8 to 14% of IE (Konstantinou, 2009; Murdoch, 2009).

30% of IE (ESC, 2009) has at least one vascular or immunological phenomenon. Vascular phenomenon includes systemic arterial embolism (17-33%) (AEPEI, 2002; Murdoch, 2009), infectious embolism (septic pulmonary infarct, infectious aneurysm) and classically Janeway lesions. Immunological manifestations are mainly represented by Osler's nodes and Roth spots (2%) (Murdoch, 2009).

Musculoskeletal symptoms are common with mainly arthralgia (14%) (Murdoch, 2009), myalgia and back pain. In the presence of, spondylodiscitis (3-15%) (ESC, 2009) mainly observed in streptococci IE must be systemically discussed. Splenomegaly is less frequently noticed (11%) (Murdoch, 2009).

4.2 Laboratory studies

4.2.1 Biology findings

- Inflammatory syndrome

In most cases, unspecific inflammatory syndrome is observed, including neutrophils hyperleucocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein.

- Microbiological diagnosis

Three sets of blood cultures, including at least one aerobic and one anaerobic samples and spaced of at least 30 minutes, should be obtained from a peripheral vein before beginning any antimicrobial therapy. The blood cultures are positive in 85% of cases (ESC, 2009). However, blood culture can be negative in cases of prior antibiotherapy or specific microorganisms (Table 3). In this last case, other bacteriological investigations are performed, such as serologies, specific PCR and culture on surgical material, catheter and device (pacemaker, defibrillator…) or embolus samples.

Negative blood culture	
Frequently	Constantly: bacteria intracellular
Fastidious Gram-negative bacilli of HACEK group Nutritionally variant streptococci Brucella Fungi	Coxiella burnetii Bartonella Chlamydia Trophynema whipplei

Table 3. Microorganisms and negative blood culture. HACEK group: Haemophilus (parainfluenzae, aphrophilus, paraphrophilus and influenza), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella (kingae and dentrificans).

- Rheumatoid factor is an immunological phenomenon, not specific but found in 5% of IE (Murdoch, 2009).

4.2.2 Histologic findings

Valvular histology after cardiac surgery is the gold standard for diagnosis of IE and observed vegetations, microorganisms and/or valvular inflammation (Greub, 2005).

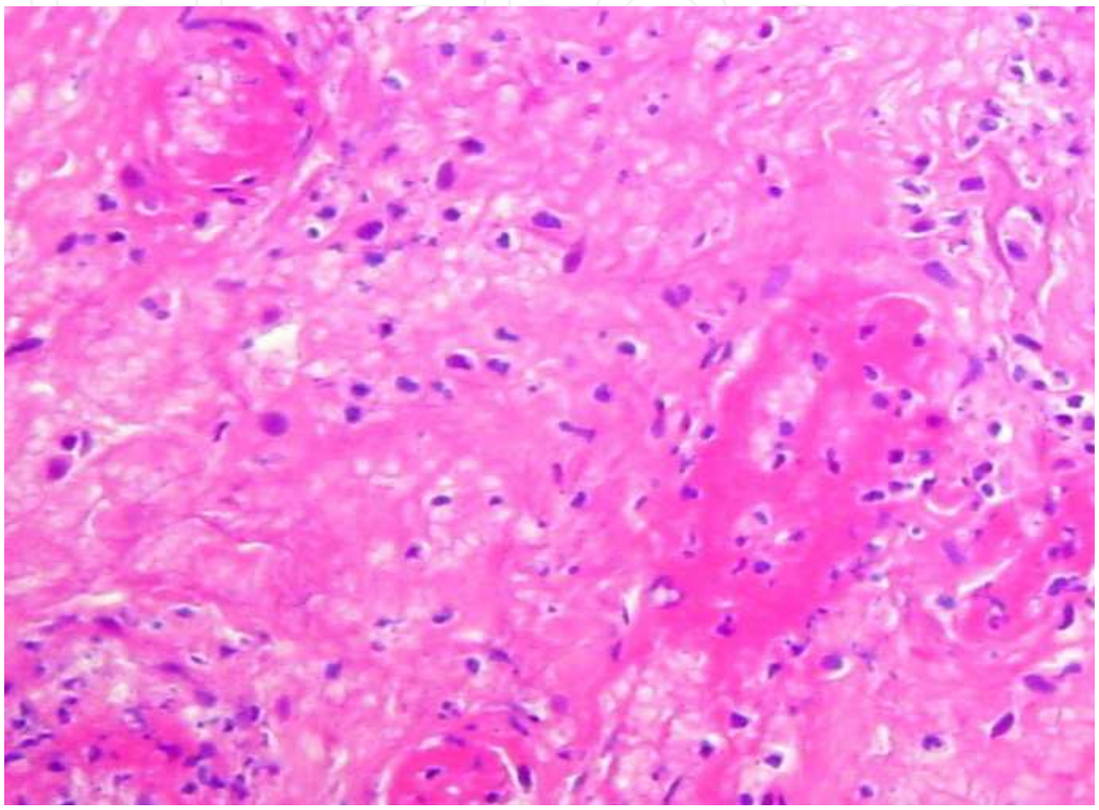

Fig. 4. Cutaneous leucocytoclastic vasculitis (H&E stain; x200).

Kidney fragments can reveal different unspecific lesions including glomerulonephritis or interstitial lesions.

Skin biopsies for histological study are often performed. Osler's nodes are classically explained by immune complex deposition, mainly responsible of leucocytoclastic vasculitis. Janeway lesions are associated with septic emboli; however, all histological findings can be observed in both lesions (Cardullo, 1990; Kerr, 1979; Loewe, 2009; Espinosa Parra, 2002).

4.3 Imaging studies

4.3.1 Echocardiography

Echocardiography is the second fundamental examination for IE diagnosis and its heart complications. In first-line, transthoracic echocardiography (TTE) must be systematically performed in case of suspicion. Its sensibility only ranges from 40 to 63%. So, in cases with

negative examination, poor quality of the exam, prosthetic valve… transoesophageal echocardiography (TEE) is recommended if there is high clinical suspicion. In the other cases, a second echocardiography must be performed 7-10 days later if suspicion remains (ESC, 2009). Evocative signs of IE are vegetations (mobile echogenic masses implanted in the endothelium in the trajectory of valvular regurgitation or implanted in prosthetic material), abscess and new dehiscence of a valvular prosthesis (Evangelista, 2004). However, echocardiography does not permit differentiation between septic and aseptic vegetations; so lesions persisting after effective treatment must not be interpreted as a clinical recurrence of the disease unless supported by clinical features and bacteriological evidence.

Echocardiography is repeated as soon as new complications are suspected or at completion of antibiotic therapy for evaluation of cardiac and valve function.

4.3.2 Other imaging

Computed tomography can be used in second intention to diagnose (good evaluation of valvular abnormalities) IE (Feuchtner, 2009) and its systemic complications.

Magnetic resonance imaging is also useful for detection of complications such as cerebral emboli.

4.4 Duke criteria

Various manifestations of IE exist and diagnosis is often difficult. Therefore, the Duke criteria combining clinical and biological criteria have been proposed (Table 4) (Li, 1999).

5. Differential diagnoses

IE is an insidious disease associated with a clinical polymorphism. Differential diagnoses are multiple and it is impossible to give an exhaustive list. Suspicion of IE must be systematically discussed in cases of unexplained fever until proof of contrary. Note echocardiographic differential diagnoses: aseptic vegetations in Libman-Sacks endocarditis (in systemic lupus erythematosus and antiphospholipid syndrome) and marantic endocarditis associated with gastric and pulmonary adenocarcinoma.

6. Severe complications

6.1 Morbidity

6.1.1 Heart complications

Heart failure is the most frequent complication (50 to 60% of IE) mainly on aortic native valve IE (29%). It can be explained by valve insufficiency after native valve destruction causing acute regurgitation (chordal rupture, leaflet rupture or perforation) or prosthesis dehiscence. Other causes of heart failure include intracardiac fistulae, myocarditis, pericarditis (in *S. aureus* infection mainly) or valve obstruction by big vegetations. Surgery is often indicated (Table 5) in emergency because this complication is the worst predictive factor of in-hospital and 6-month mortality.

Definition of term used				
Pathologic criteria		**Microorganisms** demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen		
		Pathologic lesions showing active IE: vegetation or intracardiac abscess confirmed by histologic examination		
Clinical criteria	Major criteria	**Blood culture positive for IE**	Typical microorganisms consistent with IE from 2 separate blood culture	• Viridans streptocci • *Streptococcus bovis* • HACEK group • *Staphylococcus aureus* • Community-acquired enteroccoci in the absence of a primary focus
			Microorganisms consistent with IE from persistently positive blood culture	At least 2 positive cultures of blood samples drawn > 12h apart
				All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1h apart)
			Single positive blood culture for *Coxiella burnettii* or antiphase I IgG antibody titer >1:800	
		Evidence of endobacterial involvment	Echocardiogram positive for IE TEE recommended in patients with prosthetic valves rated at least "possible IE" by clinical criteria or complicated IE (paravalvular abscess) TTE as first test in others patients	Oscillating intracardiac mass on valve or supporting structures in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation
				Abscess
				New partial dehiscence of prosthetic valve
			New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)	
	Minor criteria	Predisposition, predisposing heart condition or injection drug use		
		Fever, temperature >38°C		
		Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhages, Janeway's lesion		
		Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatic factor		
		Microbiological evidence: positive blood culture but does not meet a major criterion, serological evidence of active infection with organism consistent with IE		
Definition of IE				
Definite IE		Pathologic criteria		≥1
		Clinical criteria		2 major criteria
				1 major + 3 minor criteria
				5 minor criteria
Possible IE		1 major + 1 minor criteria		
		3 minor criteria		
Rejected		Firm alternative diagnosis explaining evidence of IE		
		Resolution of IE syndrome with antibiotic therapy for ≤ 4 days		
		No pathologic evidence of IE at surgery or autopsy, with antibiotic therapy for ≤ 4 days		
		Does not meet criteria for possible IE as above		

Table 4. Modified Duke criteria (Li, 1999) (TEE: transesophageal echocardiography; TTE: transthoracic echocardiography)

Perivalvular complications should be suspected in case of persistent fever, unexplained or occurrence of atrioventricular block. They included abscess (most common in aortic and prosthesis IE), pseudoaneurysms, fistulae and signed uncontrolled infection. *Staphylococcus aureus* is most often implicated. Despite surgical treatment, 41% of patients die during hospitalization (ESC, 2009).

6.1.2 Uncontrolled infection

Resistant microorganisms, persisting systemic infection, other sites of infection, septic shock etc … can explain locally uncontrolled infection leading to acute coronary syndrome and third degree atrioventricular block. Indication of surgery should be discussed in these cases. Persisting fever, after 7-10 days of antibiotherapy, may discuss uncontrolled infection, adverse reaction to antibiotic, perivalvular complication, thrombosis, emboli… A complete infectious investigation with blood sample examination and intravenous line replacement and cultures, should be performed as well as echocardiography.

6.1.3 Systemic embolism

Migration of cardiac vegetations is responsible for systemic embolism (20-50% of IE) mainly in brain and spleen in left-sided IE and lung in native right-sided and pacemaker lead IE (ESC, 2009). However, all organs can be affected in case of patent foramen ovale. Embolisms are not uncommonly silent (20%) and often life-threatening. The incidence of embolic events increases during the first 2 weeks after the onset of antibiotherapy. Risk factors of embolism are individualized (Table 5) and prompt antibiotherapy can limit its occurrence (Thuny, 2005). Addition of antithrombotic therapy (thrombolytic drugs, anticoagulant or antiplatelet therapy) doesn't appear helpful in preventing whereas cardiac surgery during the first week of antibiotherapy (embolic risk peak) seems beneficial.

Risk factors of embolism		
Vegetation characteristics	Location	Mitral valve
		Multivalvular IE
	Size	>10mm
	Mobility	Increasing or decreasing under antibiotherapy
Microorganisms	Bacteria	Staphylococci
		Streptococcus bovis
	Fungi	*Candida spp*
Past history	Previous embolism	
Biology	Elevated C-reactive protein	

Table 5. Risk factors of embolism in IE (Durante Mangoni, 2003; ESC, 2009)

6.1.4 Neurological complications

Neurological damages after vegetation embolism are observed in 20 to 40 % of IE, mainly due to *Staphylococcus aureus* infection. These complications include stroke, infectious aneurysm (or mycotic aneurysm), brain abscess, meningitis, toxic encephalopathy and

seizure and are associated with poor prognosis (mainly ischaemic or haemorragic strokes) (ESC, 2009; Thuny, 2007). Cerebral imaging (computed tomography or better magnetic resonance imaging) should be performed in the presence of neurological signs or headaches (infectious aneurysm).

Only poor neurological prognostic factors (coma, severe comorbidities and severe brain damage) can prohibit cardiac surgery (Table 5). In case of haemorragic stroke, cardiac surgery must be postponed for at least 1 month. In emergency cardiac situation, cooperation with neurosurgeon is mandatory. The best way to prevent these complications is to quickly start antibiotherapy (ESC, 2009).

For patients with previous antithrombotic treatment and in the absence of stroke, oral anticoagulant therapy should be replaced by unfractionned heparin for a period of 2 weeks, mainly in case of *S. aureus* IE (higher risk of bleeding). In case of an ischaemic stroke, the same schema of replacement is proposed. Anticoagulation has to be stopped in case of a haemorragic stroke and a mechanical valve; unfractionned heparin should be reinitiated as soon as possible. Previous antiplatelet therapy must be stopped only in the occurrence of major bleeding (ESC, 2009).

6.1.5 Metastatic infection

Infectious aneurysms (3% of IE) (AEPEI, 2002) are secondary to arterial septic embolism, mainly in the brain. Most of them are silent but rupture is associated with poor prognosis. No predicting factor has been individualized, however treatment (neurosurgery or endovascular surgery) is proposed in case of large, enlarging or already ruptured aneurysms. After specific antibiotherapy, most of unruptured infectious aneurysms resolve.

Systemic abscesses (other than cerebral) are rare and should be suspected in case of persistent fever and bacteremia. Clinical criteria and imaging investigation help to find the site of the infection s (tomography, ultrasound etc). Treatment can be completed by surgery or percutaneous drainage in case of partial response to antibiotics. All organs can be affected: spleen, bone (spondylodiscitis 3-15%) etc (ESC, 2009).

6.1.6 Renal complications

Acute renal failure is frequent (30%) but often reversible. Causes are multiple: glomerulonephritis by immune complex deposition, renal infarction, haemodynamic impairment and antibiotic or contrast agent toxicity (ESC, 2009).

6.1.7 Recurrences: Relapses and re-infections

Relapse is mainly observed after inadequate antibiotic treatment (insufficient duration, resistant microorganisms, empirical antibiotherapy in IE with negative blood culture) or persistent focus of infection. Conversely, re-infection is a new IE with different microorganism(s) and mainly includes patients with previous IE, intravenous drug abusers, prosthetic valve carriers and chronic dialysis patients. Re-infection increases risk of death and of valve surgery (ESC, 2009).

6.2 Mortality

In-hospital mortality varies from 9.6 to 26%. Prognosis is influenced by many factors (Table 6) but the mortality is higher (79%) in presence of heart failure associated with periannular complications and Staphylococcus infection (Chu, 2004; ESC, 2009). Operative mortality is also significant (16%) mainly in patients with prosthetic valves (Fayad, 2011).

Predictors of a poor prognostic			
Patient characteristics	Presence of complications	Microorganisms	Echocardiographic findings
- Older age - Prosthetic valve IE - Previous IE (= reinfection) - Insulin-dependent diabetes mellitus - Comorbidities	- Heart failure - Renal failure - Stroke - Septic chock - Periannular complications	- *S. aureus* - Fungi - Gram-negative bacilli	- Periannular complications - Severe left-side valve regurgitation - Low left-ventricular ejection fraction - Large vegetation - Severe prosthetic dysfunction - Premature mitral valve closure and other signs of elevated diastolic pressure

Table 6. Predictors factor of a poor prognosis in IE (ESC, 2009)

7. Treatment: Prolonged antimicrobial therapy and infectious source eradication

7.1 Medical treatment

Medical treatment should be started quickly after carrying out of bacteriological samples, in particular blood cultures (3 independent sets at 30 minutes intervals). Antimicrobial therapy is first empirical (Table 7) and as soon as possible, it is adapted to micro-organism sensitivity (ESC, 2009). In all the cases, this treatment should be prolongated for several weeks and toxicity should be followed-up. As soon as possible, portal of entry and complications should be found and treated. Symptomatic care is usual and classical.

7.2 Surgical treatment

Cardiac surgery is often necessary to treat or prevent complications or eradicate infectious sites (Table 8). Surgery is more frequently necessary in some types of IE such as native valve IE (87% of IE operated with 57% in aortic IE and 50% for mitral IE), Staphylococci and Streptococci IE (respectively 35 and 33% of IE operated) (Fayad, 2011).

With the exception of an emergency, extracardiac infections must be eradicated before surgery. Coronary angiography is also recommended in patients at risk (men older than 40, post-menopausal women, patients with at least one cardiovascular risk factor or a history of coronary disease) excluding emergency or cases with large aortic vegetation (risk of dislodgment during examination). Repair and replacement of the valve are possible but the last technique is preferred in complex cases. Intra operative transoesophageal

echocardiography is precious to guide surgeons. The operative mortality is moderate (16%) and is more frequent with prosthetic valve carriers (ESC, 2009).

Characteristics of patient		Antibiotherapy suggested for adults patients		
		Association of antibiotics	Dosage	Duration (weeks)
• Native valve or • Prosthetic valve since more than 12 months		Ampicillin-sulbactam IV	12g/day (in 4 doses)	4-6
		Gentamicin IV or IM	3mg/kg/day (in 2 or 3 doses)	4-6
	Allergy to β-lactams	Vancomycin IV	30mg/kg/day (in 2 doses)	4-6
		Gentamicin IV or IM	3mg/kg/day (in 2 or 3 doses)	4-6
		Ciprofloxacin	1000 mg/day (in 2 doses) po or 800mg/day (in 2 doses) IV	4-6
Prosthetic valve since less than 12 months		Vancomycin IV	30mg/kg/day (in 2 doses)	6
		Gentamicin IV or IM	3mg/kg/day (in 2 or 3 doses)	2
		Rifampicin po	1200mg/day (in 2 doses)	2

Table 7. Proposed antibiotic regimens for initial empirical treatment (po: *per os*/ IM: intramuscular/ IV intravenous). Be careful with chronic use of gentamicin and vancomycin. Serum levels of these antibiotics should be measured once a week for both and additional renal function testing should be performed for gentamicin.

7.3 Follow-up

Complications are usual and should be searched for regularly. This requires a daily clinical examination during the first weeks. Electrocardiogram should be performed frequently (mainly in aortic or prosthesis IE) looking for new atrioventricular block or ischemia signs. Bacteriological samples should be analyzed until their negativity. Heart failure and death can occur after several months, so echocardiography is recommended in case of cardiological signs but also after antibiotic treatment and should be repeated regularly during the first year (at 1, 3, 6 and 12 months) (ESC, 2009).

Recurrence is frequent. Consequently, patients should be informed about this risk and prevention rules should be applied closely.

8. Prevention

8.1 Antibiotic prophylaxis

In recent years, antibiotic prophylaxis has become more and more limited. In fact, no antibiotic permit disappearance of bacteremia after at-risk at-risk procedures. Until now, no study has proven the benefit of prophylactic treatment in the prevention of IE. At present, only antibiotic prophylaxis is recommended by ESC (ESC, 2009) for highest risk dental procedures in patients with highest risk cardiac conditions (Table 9). AHA (AHA, 2007) also recommends antibiotic prophylaxis for procedures on the respiratory tract or on infected skin in patients with highest risk of IE. Prophylaxis is associated with a small risk of death by anaphylaxis but no case has been reported to date and the main risk is microbial resistance development.

Indications			Location of IE		
			Left-sided native valve IE	Prosthetic valve IE (PVE)	Right-sided IE
Heart complications	Heart failure	+	Severe acute regurgitation or valve obstruction causing refractory oedema pulmonary or cardiogenic shock	Severe prosthetic dysfunction (dehiscence or obstruction)	Right heart failure secondary to severe tricuspid regurgitation with poor response to diuretic therapy
			Emergency	Emergency	
			Fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema or shock		
			Emergency		
			Severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (early mitral closure or pulmonary hypertension)	Severe prosthetic dysfunction and persisting heart failure	
			Urgent	Urgent	
		-	Severe regurgitation and no heart failure	Severe prosthetic dehiscence without heart cardiac	
			Elective	Elective	
Uncontrolled infection			Locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation)		Microorganisms difficult to eradicate (persistent fungi…) or bacteremia for > 7 days (*S. aureus, P. aeruginosa*…)
			Urgent		
			Persisting fever and positive blood cultures > 7-10 days		
			Urgent		
			Fungi or multiresistant organisms		
			Urgent / Elective		
				Staphylococci or Gram negative bacteria (most of cases of early PVE)	
				Urgent/Elective	
Prevention of embolism			Large vegetation (>10mm) following one or more embolic episodes despite appropriate antibiotic therapy	Recurrent emboli despite appropriate antibiotic treatment	Persistent tricuspid valve vegetation > 20mm after recurrent pulmonary emboli with or without concomitant heart failure
			Urgent	Urgent	
			Large vegetation (>10mm) and other predictors of complicated course (heart failure, persistent infection, abscess)		
			Urgent		
			Isolated very large vegetation (>15mm)		
			Urgent		

Table 8. Indications and timing of surgery (ESC, 2009). Emergency: within 24 hours. Urgent: within a few days. Elective: after 1 -2 weeks of antibiotic treatment.

<table>
<tr><th>Cardiac conditions at highest risk of IE</th><th colspan="2">Dental procedures at high risk</th></tr>
<tr><td rowspan="2">• Prosthetic cardiac valve or material used for cardiac valve repair
• Previous IE
• Some congenital heart disease (CHD)
• Cyanotic CHD
- without surgical repair or
- with residual defects, palliative shunts or conduits
• CHD with complete repair with prosthetic material whether placed by surgery or by cutaneous technique, up to 6 months after the procedure
• CHD when a residual defect persists at the site of implantation of a prosthetic material or device by cardiac surgery or percutaneous technique</td><td colspan="2">• Manipulation of gingival region
• Manipulation of periapical region of the teeth
• Perforation of oral mucosa</td></tr>
<tr><td colspan="2">Antibiotic prophylaxis</td></tr>
<tr><td colspan="2">Single dose 30-60 minutes before procedure</td></tr>
<tr><td>• Adults
• Amoxicillin 2g po or IV
• If allergy: Clindamycin 600mg po or IV</td><td>• Children
• Amoxicillin 50mg/kg po or IV
• If allergy: Clindamycin 20mg/kg po or IV</td></tr>
</table>

Table 9. Recommendations for antibiotic prophylaxis of IE for patients undergoing dental procedures (ESC, 2009) (po: *per os*/ IV: intravenous)

8.2 Hygienic rules

Most IE occurs without history of procedure more at-risk situation of bacteremia (Strom, 1998).

Daily activities like chewing or tooth brushing carry transient but significant bacteremia and can cause IE (AHA, 2007). Consequently, it is recommended to maintain a good oral hygiene for all population.

For patients and drug users, disposable intravenous material is mandatory.

8.3 Others rules

In medical practice, percutaneous iatrogenic procedures should be avoided especially on skin injuries and topical corticosteroid should be used with caution. Regular bacteriological skin analysis is recommended during the follow-up of erosive dermatosis because it allows quick adapted antibiotherapy in the case of secondarily advent IE. Of course, all prospective portals of entry and all comorbidities have to be searched and supported.

9. Conclusion

Infective endocarditis (IE) is a severe disease the diagnosis of which remains difficult due to clinical polymorphism and frequent insidious evolution over several days or months. Skin manifestations are very useful for diagnosis but should alert practitioners for presence of embolic complications. Epidemiologic profile of IE has changed in recent years and so has

prophylactic and therapeutic recommendations. IE concerns all practitioners and we have to keep it in mind with any patient.

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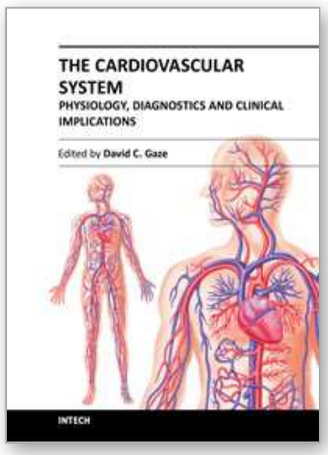

The Cardiovascular System - Physiology, Diagnostics and Clinical Implications

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The cardiovascular system includes the heart located centrally in the thorax and the vessels of the body which carry blood. The cardiovascular (or circulatory) system supplies oxygen from inspired air, via the lungs to the tissues around the body. It is also responsible for the removal of the waste product, carbon dioxide via air expired from the lungs. The cardiovascular system also transports nutrients such as electrolytes, amino acids, enzymes, hormones which are integral to cellular respiration, metabolism and immunity. This book is not meant to be an all encompassing text on cardiovascular physiology and pathology rather a selection of chapters from experts in the field who describe recent advances in basic and clinical sciences. As such, the text is divided into three main sections: Cardiovascular Physiology, Cardiovascular Diagnostics and lastly, Clinical Impact of Cardiovascular Physiology and Pathophysiology.

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