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Approach To Investigating Blood Culture-Negative Endocarditis (BCNE)

PathCare Introduces A New Multiplex PCR Panel To Detect Tick-Borne Pathogens

BACKGROUND

Infective endocarditis (IE) is a globally prevalent condition associated with high morbidity and mortality [1,2]. Although historically rare, the annual estimated incidence has increased to 13.8 cases per 100 000 patients, attributable to an increased incidence of degenerative valve disease, intravenous drug use and healthcare-associated invasive procedures [1-3]. Despite being uncommon, the diagnosis and management require extensive investigations, and treatment is prolonged, requiring more than one antibiotic targeting the cultured organism. When routine blood cultures fail to isolate the causative organism, known as "Blood Culture-Negative Endocarditis (BCNE)", diagnosis and treatment become particularly challenging, often leading to poorer outcomes [2-4].

The prevalence of BCNE varies by geographical area and the socio-economic context. In South Africa, more than a third of cases are noted to be culture negative [2,4,5]. This is commonly due to antibiotic administration before appropriate culture collection, suboptimal culture collection techniques and the presence of fastidious, slow-growing or non-culturable zoonotic organisms. Rarely, non-infectious endocarditis may occur, as a diagnosis of exclusion, in the setting of autoimmune disease such as SLE, anti-phospholipid syndrome, cardiac tumours, underlying malignancy or in those with hypercoagulable states.

Tick-borne and other zoonotic infections are an increasingly recognised but frequently underdiagnosed cause of BCNE, particularly in settings with significant animal and vector exposure such as Southern Africa. Pathogens including *Coxiella burnetii*, Bartonella spp. and Rickettsia spp. are fastidious or non-culturable using standard blood culture techniques and therefore commonly present as culture-negative disease. These infections often have a subacute and non-specific clinical course and require targeted serological or molecular testing for diagnosis. Failure to consider these organisms may delay appropriate treatment and contribute to the poorer outcomes observed in BCNE.

INVESTIGATION OF SUSPECTED BCNE

1. Culture-based methods

An astute history-taking, in combination with positive blood cultures and suggestive echocardiography, remains the optimal method for diagnosing and treating IE. Enquire about specific epidemiological links and risk factors, including exposure to animals (pets and livestock), occupation and dietary habits, e.g. ingesting unpasteurized milk.

When cultures remain negative, the following should be considered:

i. Collect blood cultures optimally.
   - Before any antibiotics are administered
   - Obtain as soon as symptoms occur
   - Collect two or more sets (each set comprising 1 aerobic and 1 anaerobic culture) [3,6]
   - Each bottle should contain 8-10mL of blood [3]

ii. Alert the laboratory that IE is suspected.
   - This ensures prolonged incubation of cultures (e.g. fungal cultures require extended incubation)
   - Alerts laboratory personnel to be observant for organisms that pose a biosafety threat (e.g. Brucella species) or fastidious organisms (e.g. HACEK group).
   - Prompts the laboratory to consider PCR testing, now recognized as a major criterion for IE diagnosis [4,6]

iii. If antibiotics were administered before culture: Consider ceasing antibiotics and repeating blood cultures in stable patients with subacute symptoms, no evidence of local or distant complications, and receiving a very short course of antibiotics [1]

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2. Non-culture-based methods

Test	Sample type	TAT ♗	Request code	Diagnostic method
Serology	Serum sample 1 x SST	4 days	ZSBARHENG ZSBARHENM ZSBARQUIG ZSBARQUIM	*Bartonella henselae and B. quintana* IgG and IgM# [Titres performed if antibodies detected]
		48hrs	SQF	*Coxiella burnettii* (Q-Fever) IgM Phase I/II and IgG Phase I/II [Titres performed if antibodies detected]
		24-48hrs	SBRUC	*Brucella abortus,* IgG and IgM
	Serum sample 1 x SST	4 days	SAGAL	Serum galactomannan (Suggests Invasive Aspergillosis, not diagnostic)
	Serum sample 1 x SST	24-48hrs	SBETA	Serum (1,3)-beta-D-glucan (Fungitell) (Suggests Invasive Candidiasis, not diagnostic)
Molecular/ PCR	Tissue* or Prosthetic valve	24-48hrs	PPCRRIC M2328	Tick-borne disease Multiplex PCR panel
		2-5 days	PM16SRRNA/ PMFUNGI	PanBacterial PCR (16S PCR)/ PanFungal PCR
	EDTA Whole Blood	24-48hrs	PPCRRIC M2328	Tick-borne disease Multiplex PCR panel
		24-48hrs	PPCRRIC M2328	Qualitative PCR for specific aetiology *(Brucella species)*
Other rare causes to consider				
Slow growing and rapidly growing Mycobacterial ssp.	EDTA Whole Blood	2-6 weeks	MTBR	Mycobacterial blood culture
		24-48hrs	MTBR +C5057	TB investigation (TB PCR, AFB and TB culture)
		24-48hrs	SQNTTB	MTB IGRA testing
	Tissue*¶	4 days	SAGAL	Serum galactomannan (Suggests Invasive Aspergillosis, not diagnostic)
	Quantiferon tube	24-48hrs	SBETA	Serum (1,3)-beta-D-glucan (Fungitell) (Suggests Invasive Candidiasis, not diagnostic)
Chlamydia spp.	*-C. pneumoniae* *-C.trachomatis* *-C. psittaci*		Please contact your local clinical microbiologist to discuss testing options.	
Mycoplasma spp	*-M. hominis*		Please contact your local clinical microbiologist to discuss testing options.	

♗ Note: The turnaround time (TAT) illustrated in the table accommodates 'batched' and 'referred' tests, and is an estimate. Some results may be available sooner. Please discuss with your local clinical microbiologist.

#Common aetiology amongst African cohorts [3].

*Refers to native heart valve post valve replacement /endocardial tissue, both received in **normal saline** or a wound eschar from a tick bite. This can also include a swab of a skin lesion in suspected Bartonella species.

Remember to send a separate sample, in formalin, for Histopathological analysis

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PATHCARE INTRODUCES THE NOVEL TICK-BORNE DISEASE MULTIPLEX PCR PANEL

Recently, the International Society for Cardiovascular Infectious Diseases (ISCVID) proposed updates to both the major and minor criteria of the Modified Duke Criteria, reflecting a growing recognition of the diagnostic value of molecular based techniques in IE.[4,6]

In alignment with these developments, PathCare will now offer a multiplex PCR assay capable of simultaneously detecting several tick-borne pathogens, many of which are recognized causes of BCNE, while also enhancing our diagnostic capability for other clinically significant tick-borne infections, e.g. Tick-bite fever.

The assay targets include:

Rickettsia spp.	*Borrelia miyamotoi*	*Borrelia burgdorferi sensu lato complex*
Anaplasma phagocytophilum	*Ehrlichia spp.*	*Tick-borne encephalitis virus*
Babesia spp.	*Coxiella burnetii*	*Bartonella spp.*

Clinical indications:

This assay should be considered in:

- Cases of suspected infective endocarditis, where **blood cultures remain negative** after 48-72 hours of incubation.
- Cases with significant epidemiological risk factors such as **tick exposure, animal contact, or travel to endemic areas.**
- For **confirmatory diagnosis** in cases where screening serology is positive.

Specimen requirements:

- **Preferred specimens:** Tissue biopsies including cardiac valve tissue and eschars, whole blood (EDTA) and CSF
- **Minimum volume:** 3–5 mL (blood); tissue samples should be placed in sterile containers in normal saline.

This assay provides significant cost efficiencies for both patients and healthcare funders by applying a single PCR tariff to a comprehensive diagnostic panel. It enables an expanded and clinically valuable diagnostic work-up, particularly for the identification of tick-borne pathogens such as Rickettsia species, while also enhancing the investigation of blood culture–negative endocarditis. In addition, the assay is automatically performed alongside qualitative single-target requests at no additional cost, further improving cost-effectiveness and diagnostic yield.

References

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