

# Did the updated Duke criteria missed *Erysipelothrix rhusiopathiae* from the list of typical microorganisms causing infective endocarditis?

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## SUMMARY

Infectious endocarditis is a severe condition still characterized by a high morbidity and mortality rate. An early diagnosis may positively impact the outcome, so we need our diagnostic tools to match with the ever-changing epidemiologic and microbiologic landscape of infectious diseases.

We read with great interest the update to the Modified Duke Criteria for the diagnosis of Infectious Endocarditis recently proposed by the International Society for Cardiovascular Infectious Diseases and decided to propose the addition of *Erysipelothrix rhusiopathiae* to the list of typical microorganisms causing Endocarditis. This pathogen is widespread distributed in the world,

has a zoonotic origin, harbors virulence factors and a multidrug resistance phenotype. Moreover, its retrieval from blood seems to have an important correlation with the presence of Endocarditis.

The inclusion of *E. rhusiopathiae* in the list of typical microorganisms may represent a further refinement of the Modified Duke Criteria, which represent a fundamental tool in the management of patients with suspected endocarditis.

**Keywords:** *Erysipelothrix rhusiopathiae*, Erysipeloid, Endocarditis, Modified Duke Criteria.

**I**nfectious Endocarditis (IE) remains a severe condition with a high mortality rate where the prompt establishment of an adequate antibiotic therapy may improve the outcome [1]. Unfortunately, the formulation of an early diagnosis is getting more challenging due to the increasing age of occurrence, the evolving epidemiology, the misuse of antibiotics in the general population and the ever-growing prevalence of prosthetic devices [2]. Recently, the International Society for Cardiovascular Infectious Diseases (ISCVID) proposed a further update of the Modified Duke Criteria for IE diagnosis [3]. Among many relevant changes, ISCVID revised the list of typical micro-

organisms causing IE, defined as those pathogens whose isolation as bloodstream infection (BSI) agents is strongly associated with a concurrent IE, even if they do not represent a prevalent cause of IE [3]. Based on the high risk of IE in patients with bacteremia, *S. lugdunensis*, *E. faecalis*, *Granulicatella*, *Abiotrophia* and *Gemella* species and all *Streptococcus* species except for *S. pneumoniae* and *S. pyogenes* are now considered typical; on the contrary, non-faecalis Enterococci were omitted. Moreover, the new definitions consider the clinical context in which the episode of bacteremia occurs, and hence some pathogens are now typical only in the setting of intracardiac prosthetic material [3]. Considering these assumptions, we suggest the inclusion of *Erysipelothrix rhusiopathiae* in the new list of typical IE agents.

*E. rhusiopathiae* is a pleomorphic Gram-positive bacillus that ubiquitously contaminates soil and

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water and persist for a long period of time in the environment, including marine locations [4]. It is responsible for an erysipelas-like syndrome in wild and farm animals, possibly progressing to arthritis, sepsis, and IE. Substantial economic losses are associated with swine, turkey, and chicken erysipelas and with sheep polyarthritis [4]. In humans produces an occupational skin infection typical of livestock and seafood handlers, named erysipeloid, which manifests predominantly on hands as a superficial, inflammatory, painful, violaceous plaque usually self-limiting within 3-4 weeks without specific therapy [5]. Occasionally, the infection progresses causing a generalized cutaneous form and/or a systemic syndrome with BSI, hematogenous dissemination and possibly IE, that can take a fulminant course [5]. Endocarditis from *E. rhusiopathiae* appears to involve mainly native aortic and mitral valves, with a male predominance and alcohol abuse as a probable risk factor. Surgery is commonly required (about 57%) and the outcome of IE is frequently poor with a mortality rate of about 33% [6]. The evidence concerning the incidence of IE among patients with BSI from *E. rhusiopathiae* consists largely of case reports and case series, sometimes with conflicting results, while only 3 larger studies are available (Table 1). An early sys-

tematic review included 49 cases and stated that *E. rhusiopathiae* BSI may reveal the presence of an underlying IE with a very high likelihood (up to 90%) [5, 7]. This association was questioned by subsequent studies. A single-center retrospective study examined all cases of adults with *E. rhusiopathiae* BSI hospitalized in the previous 22 years. To be included patients required at least 2 simultaneous, positive blood cultures sets so that the numerosity obtained was very low (N=5). Finally, only 20% of subjects had ultrasound documented IE, but interestingly all the patients required 4-6 weeks of treatment to resolve symptoms [8]. A recent 20-year systematic review analyzed 62 cases of infections from *E. rhusiopathiae*, the majority involving adult men with an animal-related job and living in a high-income country. Hypertension, diabetes, and alcoholism were the main associated diseases. Skin lesions were the most common manifestations of infection (33,9%), followed by heart valve involvement that affected 37,1% of the cohort and 60,9% of them required valve replacement surgery [9].

By comparison (Table 1), BSI from *Staphylococcus aureus* is complicated by IE in 18,2% of cases, from *Enterococcus faecalis* in 11,5% and from *Streptococcus*-like bacteria in about 5,7% [10-12]. In a large retrospective cohort study the overall prevalence

**Table 1 - Prevalence of infectious endocarditis in patients with Erysipelothrix rhusiopathiae infection**

Pathogen	First author, year	Design	Numerosity, type of infection	Endocarditis (%)
<i>E. rhusiopathiae</i>	Gorby, 1988	Systematic review from 1912 to 1988	49 BSI	90,0
<i>E. rhusiopathiae</i>	Tan, 2017	Retrospective cohort analysis lasting 22 years	5 BSI	20,0
<i>E. rhusiopathiae</i>	Rostamian, 2022	Systematic review from 2000 to 2020	62 infections	37,1
<i>S. aureus</i>	Van der Wart, 2022	Prospective cohort study	477 BSI	18,2
<i>E. faecalis</i>	Rosselli del Turco, 2021	Review of 5 large retrospective studies	3.080 BSI	11,5
<i>Streptococcus</i> -like ( <i>Abiotrophia</i> , <i>Aerococcus</i> , <i>Gemella</i> , and <i>Granulicatella</i> )	Berge, 2019	Retrospective cohort study	558 BSI	5,7
Streptococcal species	Seo, 2023	Retrospective cohort study from 2010 to 2020 of BSI from <i>Streptococcus</i> spp.	2.737 BSI	<i>S. mutans</i> : 33 <i>S. sanguinis</i> : 31 <i>S. gordonii</i> : 23 <i>S. gallolyticus</i> : 16 <i>S. oralis</i> : 12 Overall: 6,4

Abbreviations: BSI, bloodstream infection.

of IE in patients with BSI from many Streptococcal species was 6.4%, with *S. mutans* and *S. sanguinis* displaying the higher rates (>30%) [13].

*E. rhusiopathiae* is also equipped with some important virulence factors: the release of neuraminidase causes vascular damage, a polysaccharide capsule protects from phagocytosis and some adherence proteins with specific endothelial affinity are involved in the establishment of biofilm [14]. In addition, conventional culture techniques present low yield for *E. rhusiopathiae* due to slow growth rate and frequent contamination, requiring molecular techniques to increase sensitivity and avoid false positive results [15, 16].

*In vitro* susceptibility studies identified penicillin, cephalosporin, and imipenem as the most bactericidal drugs [17]. Worryingly, *E. rhusiopathiae* is intrinsically resistant to vancomycin, teicoplanin, cotrimoxazole, aminoglycosides and rifampicin, antimicrobials that are often included in the empirical treatment of severe Gram-positive infections and IEs, especially for  $\beta$ -lactam-intolerant patients [15, 17].

So far, thanks to its stable penicillin susceptibility, this pathogen elicited low concern, but in recent times the nightmare of resistance is giving prove of itself in the context of veterinary medicine. Two *in vitro* findings on isolates collected from outbreaks of septicemic erysipelas in birds showed how this pathogen is acquiring additional resistance to commonly used molecules. Samples from poultry proved resistance to penicillin G in 42% and to erythromycin in 76%, while isolates from geese were resistant to norfloxacin in 68% and tetracycline in 63% [18, 19].

In conclusion, *E. rhusiopathiae* is a worldwide distributed, zoonotic, intrinsically glycopeptide-resistant pathogen with the potential to develop a multidrug-resistant phenotype, that harbors some dangerous virulence factors and is able to cause a severe form of IE. We recognize that evidence is still limited in quality and require larger and systematic studies but, as things stand, its recovery from blood has a likelihood of endocardial involvement higher than many pathogens that are presently regarded as typical of IE. The inclusion of *E. rhusiopathiae* in the updated list of typical IE microorganisms of the Modified Duke Criteria may constitute a further refinement of this fundamental tool for the diagnosis and management of patients with suspected IE.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

LV: original draft preparation, research and editing; AO: conceptualization, review and editing; MV: conceptualization, review and editing.

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