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### ► **To cite this version:**

Julie Plouhinec, Isabelle Rince, Eliette Riboulet-Bisson, Axel Hartke, Abdellah Benachour. Enhancement of oxidative stress improves antibiotic treatment efficiency against *Enterococcus faecium*. FEMS MICRO, Jul 2025, Milan, Italy. <hal-05563095>

**HAL Id: hal-05563095**

**<https://normandie-univ.hal.science/hal-05563095v1>**

Submitted on 23 Mar 2026

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# Enhancement of oxidative stress improves antibiotic treatment efficiency against *Enterococcus faecium*

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## Introduction

Since the 1980s, enterococci have become a **significant concern** for public health due to their capacity to cause **hospital-acquired infections (HAIs)**. The species *E. faecium* (*Efm*) is classified as a **high priority** target for the development of new therapeutic approaches because of its **multidrug resistance** (O'Toole *et al.* 2023). Currently, one of the primary therapeutic options used to treat enterococcal infections is the antibiotic **tigecycline (TIG)**, which acts as a bacteriostatic agent. Recently, Wasselin and colleagues highlighted a **link** between oxidative stress and the effectiveness of tigecycline (Wasselin *et al.* 2025). By nature, *Efm* **metabolism produces** high intracellular levels of hydrogen peroxide ( $H_2O_2$ ). This ROS is partially eliminated by a **NADH peroxidase (Npr)**. The study revealed that tigecycline is bacteriostatic when Npr is present but induces **bacterial lethality** when Npr is absent and  $H_2O_2$  exceeds a certain threshold. Based on these findings, our study aims to enhance the **effectiveness of tigecycline** by combining the antibiotic with a prooxidant molecule, **Menadione**, to make the treatment bactericidal instead of bacteriostatic (**Figure 1**).

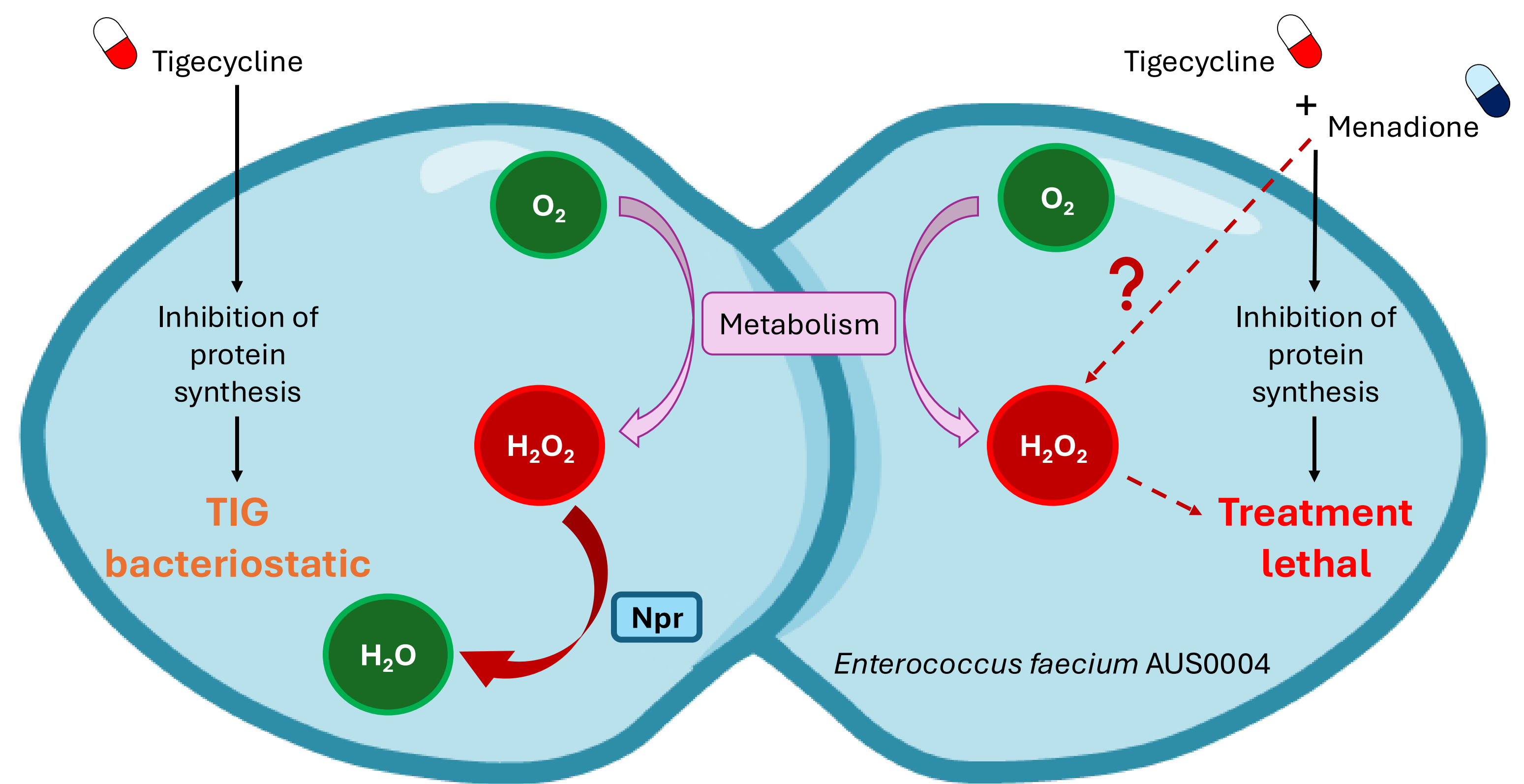
## Results

**Table 1:** Combinatorial effect of menadione and tigecycline against *Efm* strains

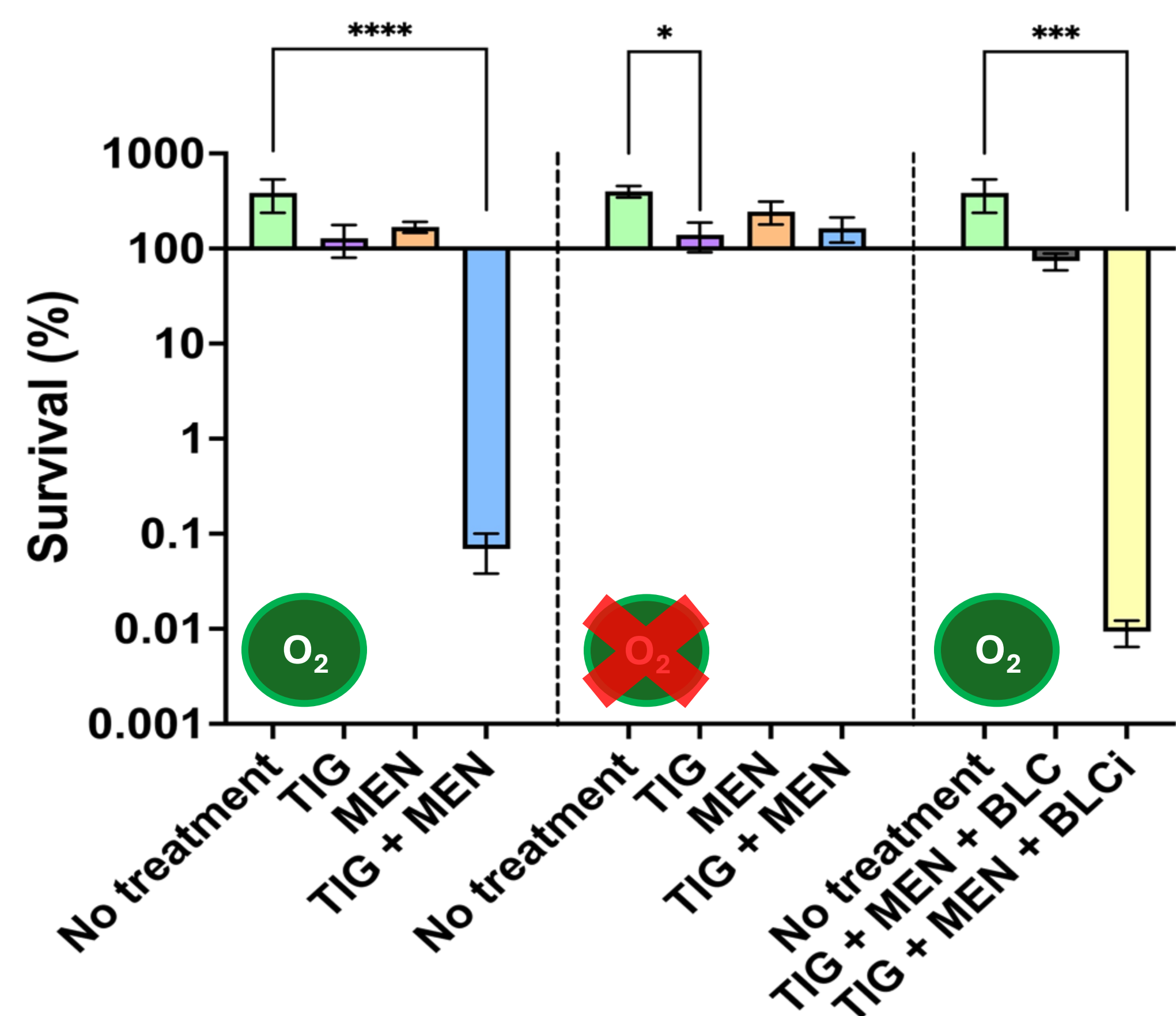
Souches	Van <sup>R/S</sup>	MIC alone		MIC combination		FIC index	Interaction
		TIG	MEN	TIG	MEN		
<i>E. faecium</i> AUS0004	Van <sup>R</sup>	0,063	2	0,031	0,4	<b>0,69</b>	ADDITION
<i>E. faecium</i> 1,230,933	Van <sup>R</sup>	0,063	0,4	0,031	0,1	<b>0,76</b>	ADDITION
<i>E. faecium</i> 1,232,502	Van <sup>R</sup>	0,031	0,4	0,004	0,2	<b>0,63</b>	ADDITION
<i>E. faecium</i> 1,141,733	Van <sup>S</sup>	0,063	0,8	0,031	0,4	<b>0,99</b>	ADDITION
<i>E. faecium</i> 1,232,501	Van <sup>S</sup>	0,063	1,6	0,004	0,8	<b>0,56</b>	ADDITION

Each value of MIC represents the most frequently observed MIC among at least three biological replicates.

- The combination of tigecycline with menadione reduces MIC of TIG against *Efm* AUS0004.
- Combining tigecycline and menadione has similar effects on other *Efm* strains.

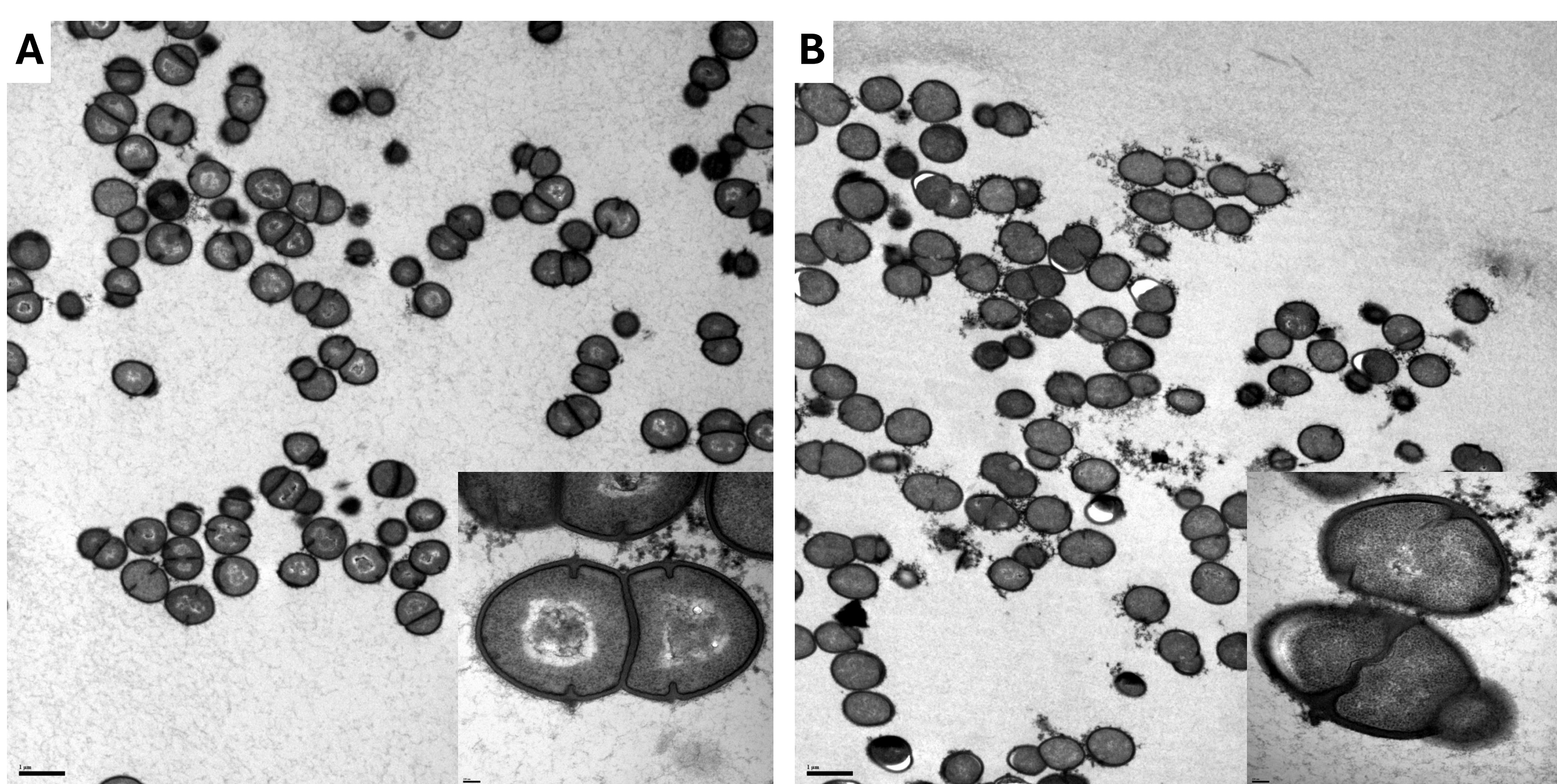


**Figure 1:** Effect of tigecycline alone or in combination with menadione on *Efm* AUS0004 strain



**Figure 2:** *E. faecium* survival (%) treated during 24 hours with **tigecycline** ( $0,1mg.L^{-1}$ ) or **menadione** ( $0,1mM$ ) alone or **combined** and with the addition of bovine liver catalase (**BLC**) at  $5000U/mL$  or inactivated (**BLCi**) under aerobic or anaerobic conditions. \* < 0,05; \*\*\* < 0,001; \*\*\*\* < 0,0001 (Kruskal-Wallis test)

- Tigecycline combined with menadione significantly impact the survival of *Efm* AUS0004.
- Oxygen and  $H_2O_2$  play a role in the mortality of *Efm* AUS0004 during a treatment of tigecycline / menadione.



**Figure 3:** Transmission electron microscopy photos of *Efm* AUS0004 after 6 hours without treatment (A) or with tigecycline / menadione treatment (B)

- The envelope integrity of *Efm* AUS0004 is altered after 6 hours of treatment.

## Conclusion

- ✓ The **combination of menadione with tigecycline** leads to **lethality** in *Efm* AUS0004
- ✓ **Efficacy** of this **treatment** depends on  **$H_2O_2$  accumulation**
- ✓ **Combinatorial treatment** has a deleterious effect on **envelope integrity** of *Efm*

**Menadione + Tigecycline improve treatment against *Efm* infections.**