L'*envelope* antibatterico per la profilassi delle infezioni della tasca

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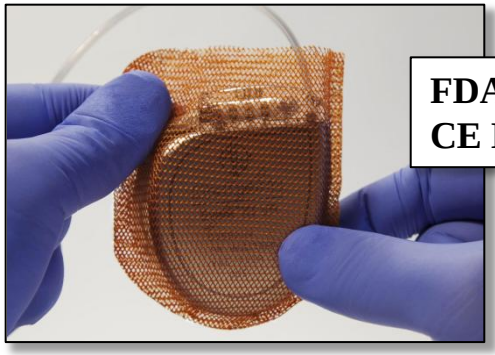
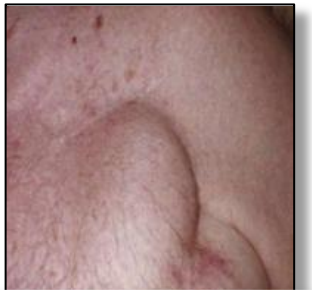
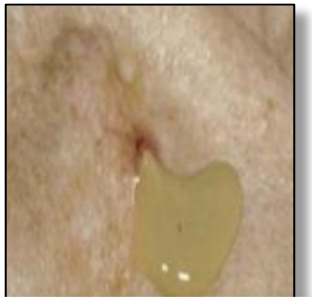
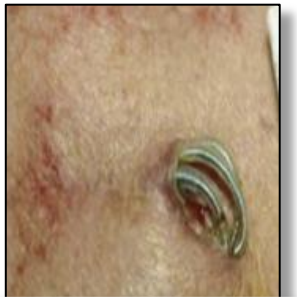
Site-specific prophylaxis of pocket infection



FDA license in May 2013
CE Mark in September 2014







60% of CIED infections are pocket infection

Latent colonization of the pocket

Europace (2010) 12, 58–63
doi:10.1093/europace/eup334

CLINICAL RESEARCH
Implantable Cardioverter-Defibrillators

Prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator patients without signs of infection undergoing generator replacement or lead revision

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Aims This study was designed to evaluate the prevalence of bacterial colonization of generator pockets in implantable cardioverter defibrillator (ICD) patients without signs of infection and to analyse the impact of bacterial colonization on the incidence of device infection during follow-up.

Methods and results In 122 ICD patients undergoing generator replacement or surgical lead revision between January 2006 and July 2008, microbiological cultures of generator pockets and extracted leads were consecutively obtained. Patients with clinical evidence of a device infection were excluded. Positive cultures from the generator pocket and leads were found in 40 (33%) patients. The most common bacteria isolated were coagulase negative staphylococci (68%). During a median follow-up time of 203 days after the revision device infection occurred in three [7.5%, confidence interval (CI) 1.6–20.4%] patients with a positive culture vs. two (2.4%, CI 0.3–8.5%) patients with a negative culture ($P = 0.33$). Time from revision to infection was 108 ± 73 days in patients with positive culture vs. 60 ± 39 days in patients with negative culture ($P = 0.50$).

Conclusion A third of ICD patients undergoing generator replacement or lead revision have an asymptomatic bacterial colonization of generator pockets. After revision 7.5% of these patients develop a device infection with the same species of microorganism.

Keywords Device infection • ICD • Swab culture

Introduction

The rate of device implantations is increasing with ageing of the general population and the formulation of new indications.[1,2] Although conferring obvious benefits, the use of these implantable devices is associated with serious complications, including infections. Reported incidence rates of cardiac device infections range from 0.13% to 19.9% and 0.0% to 3.2% for pacemakers and implantable cardioverter defibrillators (ICD), respectively.[3–8] Device replacement or repeat interventions are known to be associated with an increased rate of device infection.[9] Harcombe et al.[10] observed a five-fold increased complication rate in patients undergoing elective generator replacement compared with patients receiving first implantation of a permanent pacemaker. The most common pathogens of pacemaker/ICD infection are skin flora, including *Staphylococci* and *Corynebacteria*.[11] Although several studies have focused on the mechanism of device infection, there is a considerable uncertainty about the sources of device infection.[12,13] One pathophysiological mechanism is contamination of the pocket at the time of device implantation. Repeat interventions may reduce the patient's defence to the bacteria which might become clinically relevant after revision. Therefore, the aim of

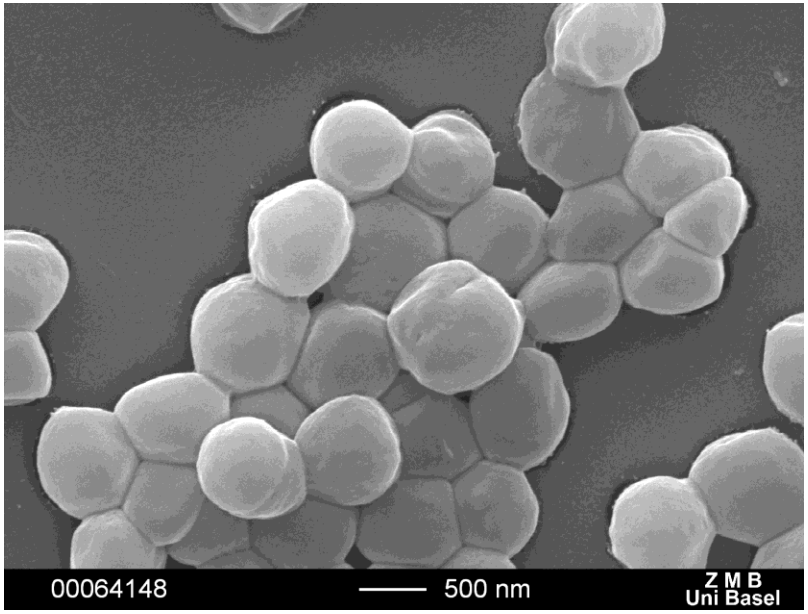
Kleemann et al_Europace 2010; 12: 58–63

≈ 35%
at the time of ICD replacement showed asymptomatic bacterial colonisation of the pocket

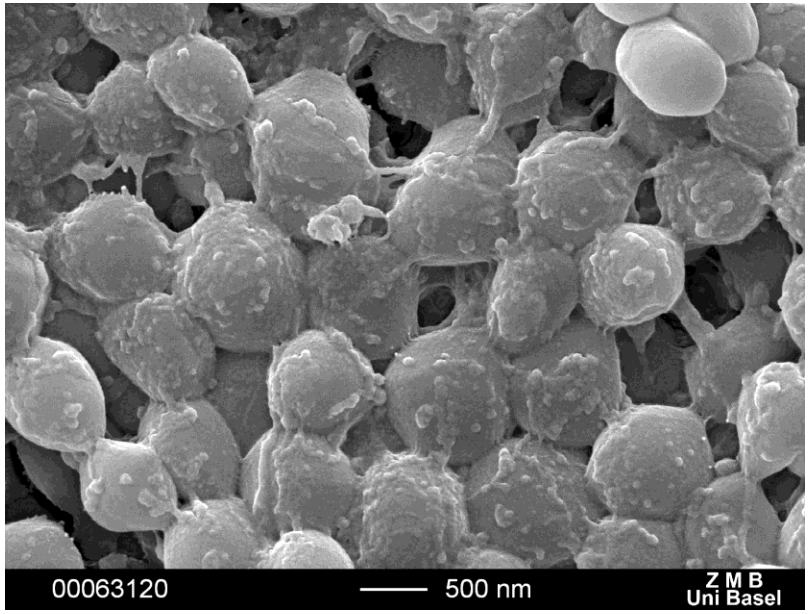
≈8%
developed device infection with the same microorganism after 3-4 months

Staphylococcus

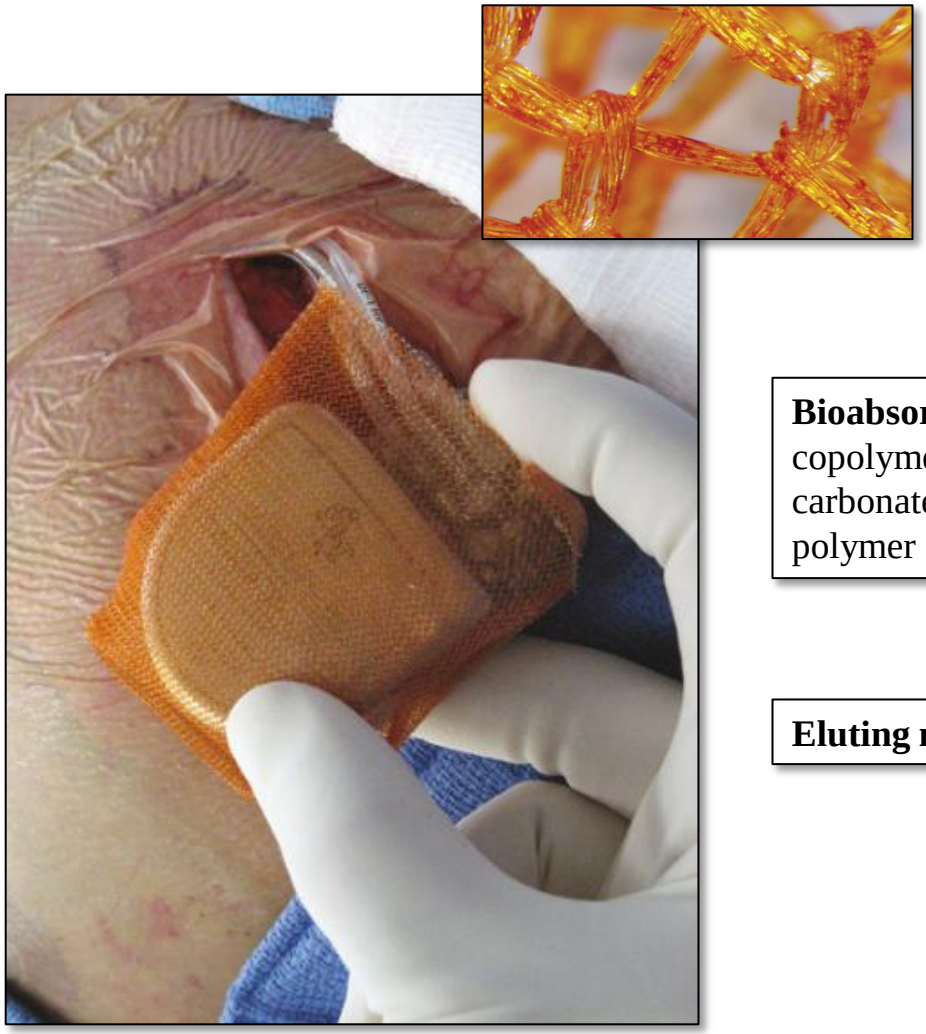
Planktonic (free-floating) mode



Biofilm mode



The TYRX Absorbable Antibacterial Envelope

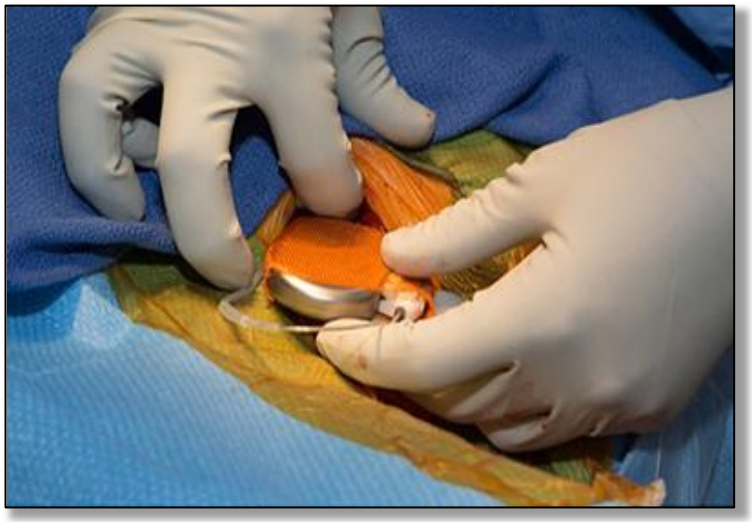


Bioabsorbable (over 9 weeks) multifilament knitted mesh copolymer made of glycolide, caprolactone and trimethylene carbonate that is coated with a bioabsorbable polyarylate polymer (tyrosin)

Eluting minocycline and **rifampin** (over 1-2 week)

Implantation technique

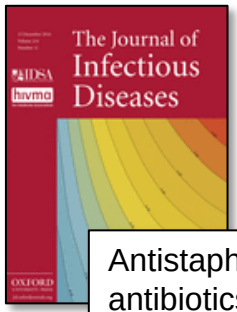
The mesh has a high **coefficient of friction**, and will require upsizing the subcutaneous device pocket 10%-15% by volume to allow ease of entry.



Inverting the TYRX to turn the seal to the inside allows easier entry of the generator

Gently moistening the sleeve immediately prior to insertion in the pocket with saline

Combination of Minocycline and Rifampin: *in vitro* model



Antistaphylococcal activity of rifampin with other antibiotics. *J Infect Dis 1981; 144:365–371*

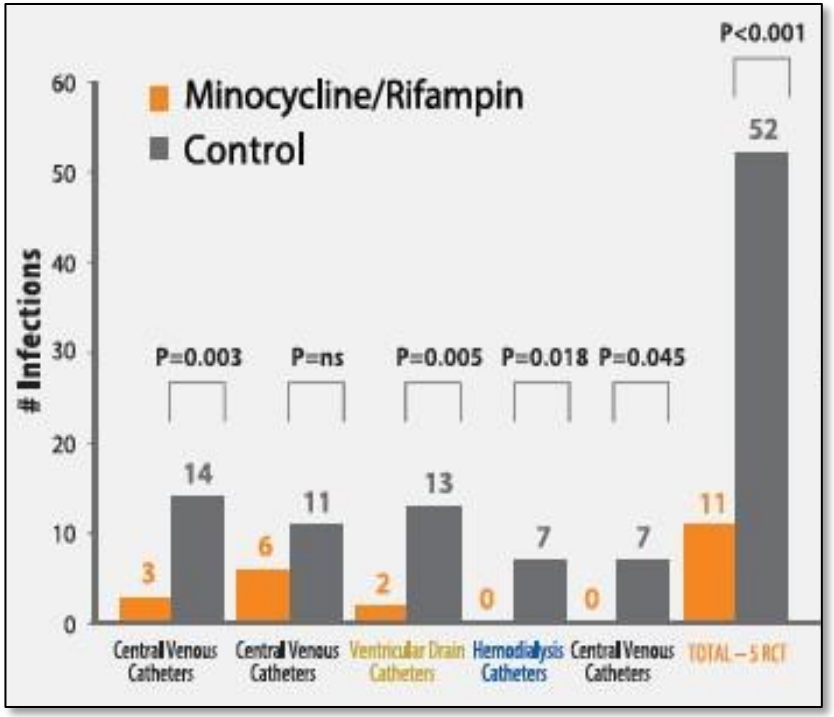
Antibiotic susceptibility of staphylococcal isolates from patients with vascular catheter-related bacteremia: potential role of the combination of minocycline and rifampin. *Int J Antimicrob Agents*

In vitro activity of minocycline and rifampin against staphylococci. *Diagn Microbiol Infect Dis 1989; 12:253–255*

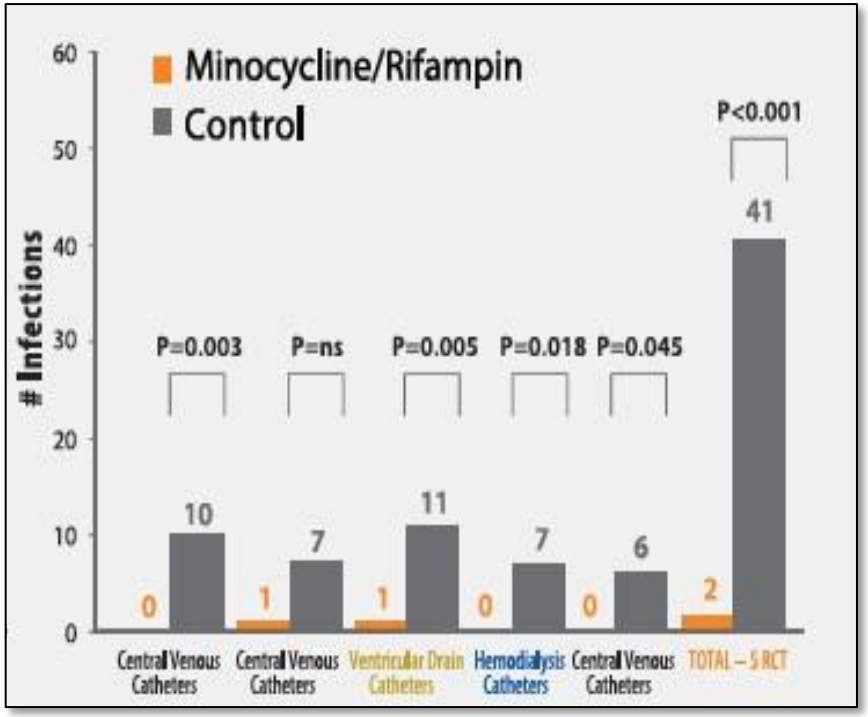
Coated MD with Minocycline and Rifampin:

- Randomised clinical studies -

Risk reduction of infection
by a factor of 4.8 (relative risk =0.2)



Risk reduction of infection caused by
Coagulase (-) Staph.* and *Staph. Aureus
by a factor of 20.6 (relative risk=0.05)



[1] Hanna H, et al. *J Clin Oncol*. 2004;22:3163-3171.
[2] León C, et al. *Intensive Care Med*. 2004;30:1891-1899.
[3] Zabramski JM, et al. *J Neurosurg.* 2003;98:725-730.
[4] Chatzinikolaou I, et al. *Am J Med*. 2003;115:352-357.
[5] Raad I, et al. *Ann Intern Med*. 1997;127:267-274.

TYRX: preclinical *in vivo* model

In Vivo Model of Human Pathogen Infection and Demonstration of Efficacy by an Antimicrobial Pouch for Pacing Devices

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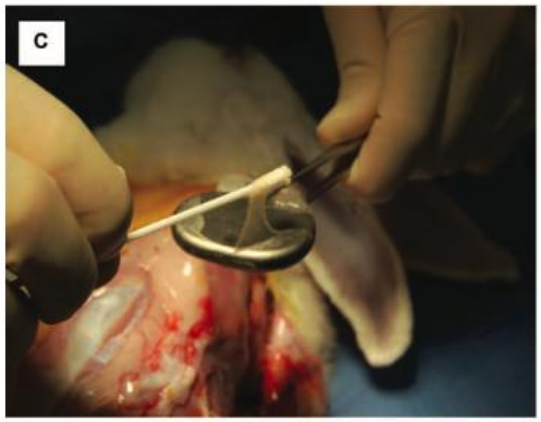
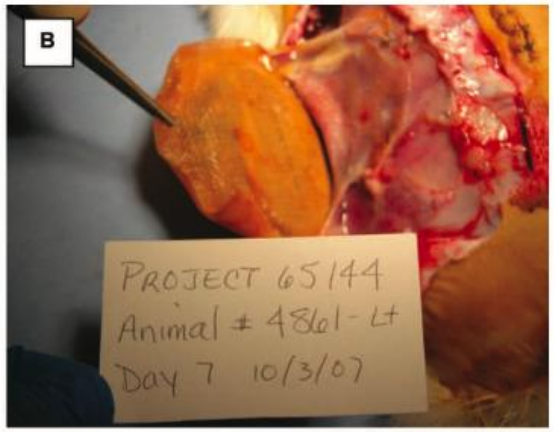
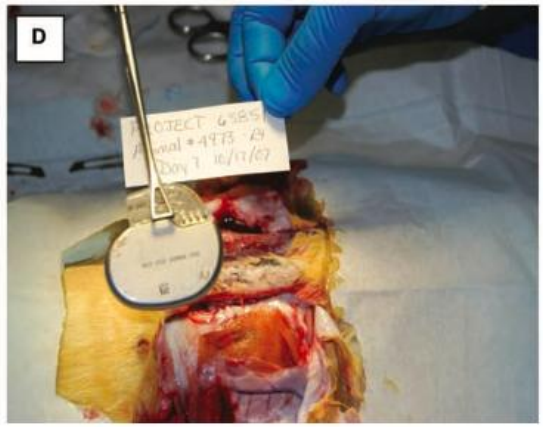
From the *WuXi AppTec, Inc., St. Paul, Minnesota; †Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University Medical Center, Columbus, Ohio; and ‡Michael E. Debakey Veterans Affairs Medical Center, Houston, Texas

Background: *Device-related infections represent a significant clinical challenge. Once established, these infections prove difficult to treat with existing antibiotic regimens, compromising the health of device recipients, and usually requiring surgical intervention to resolve.*

Objective: *The purpose of this study was to determine the efficacy of the AIGIS$_{RX}$™ antibacterial envelope (TyRx Pharma, Inc., Monmouth Junction, NJ, USA) designed to reduce device-related infections*







Biofilm

TYRX prevented *biofilm* formation

expanded indication, the use of implantable car- ...vices is likely to continue to rise. How- ...e incidence of implantable device-related ...s continues to pose significant clinical ...s. During the period 1996–2003, there was ...rise in the number of new cardiovascu- formed by low-volume centers, or even higher reporting rates due to greater awa... that CIED infections remain a crit... cern. Further, CIED infection incr... mortality more than twofold comp... cipients without infection.[2] The ... when treating such implant infections emphasize the critical need to develop improved methods of preventing the infection of implantable devices.

The most common bacterial strains involved in the etiology of cardiac device infections include *Staphylococcus aureus* (*S. aureus*), and coagulase-negative *Staphylococci* such as *Staphylococcus epidermidis* (*S. epi*). Staphylococcal species account for more than two-thirds of cardiac device

The testing presented in this manuscript was sponsored by TyRx Pharma, Inc., manufacturer of the AIGIS$_{RX}$™ product.

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PACE 2009;32:898-907

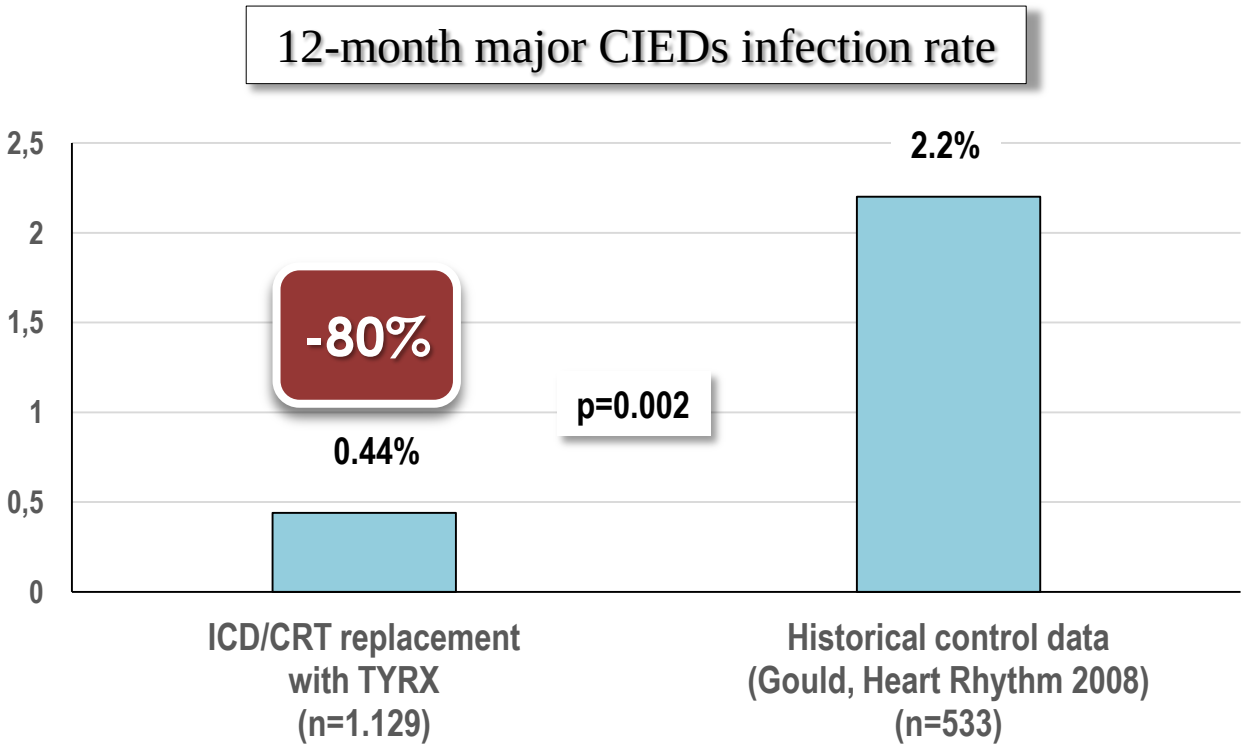
TYRX: clinical studies

More than 100.00 pts underwent CIED implantation combined with TYRX

Close to 3.000 pts have been enrolled in completed clinical studies

Non-Absorbable Antibacterial Envelope

Prospective non-randomized multicentre (66 US centers) cohort studies,1.129 patients (expected 4.300) undergoing ICD or CRT replacement from 2009 to 2014



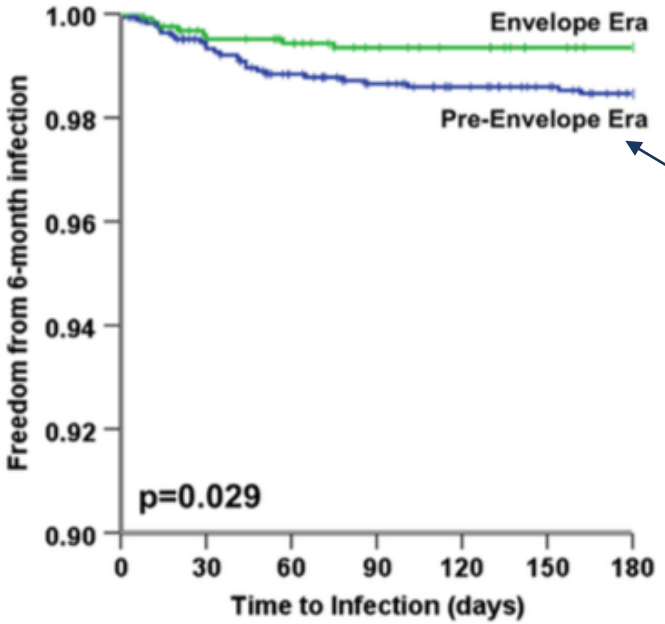
Mittal et al_Heart Rhythm 2014;11:595–601

Valley Health System Study

Non-Absorbable Antibacterial Envelope

Retrospective analysis of a large contemporary cohort of 2.891 consecutive patients in the pre-envelope era (n=1.651) and post-envelope era (n=1.240)

Freedom from 6-month infection



2010-2011

Infection rate 0.6%

2007-2009

Infection rate 1.5%

After its availability, TYRX was used at discretion of the implanting physician in 275 (22 %) of 1.240 patients deemed high risk for CIEDs infection

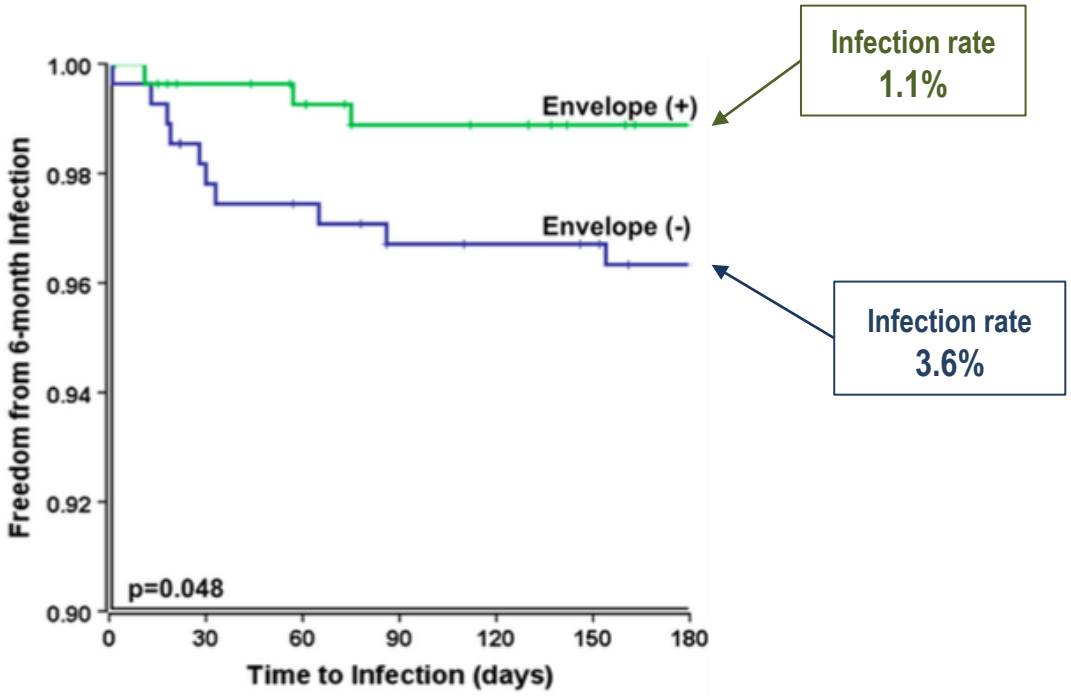
Mittal et al_Heart Rhythm 2014;11:595–601

Valley Health System Study

Propensity analysis

275 patients with TYRX matched with respect to high-risk characteristics with 275 patients in the pre-envelope era

Freedom from 6-month infection



Mittal et al_Heart Rhythm 2014;11:595–601

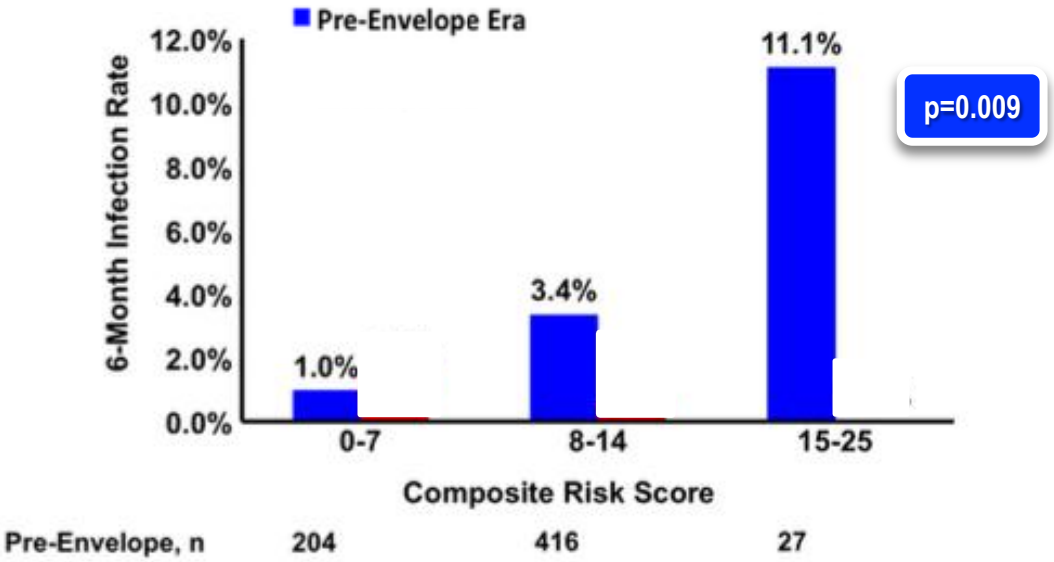
Valley Health System Study

Risk score for CIED infection

Risk factors for CIED infection

1. Diabetes mellitus
2. History of CHF
3. Male gender
4. GFR ≤60 ml/m
5. Upgrade procedures
6. Hypertension
7. Early pocket exploration (within 30 days)

6-month infection rate *



* Only patients with ICD or CRTD

Kolek et al_ J Cardiovasc Electrophyol 2015;26:111-6

Absorbable Antibacterial Envelope

Single-centre retrospective cohort study of 1.124 patients with **at last 2 risk factor** for CIED infection, from 2009 to 2014, minimum follow-up 300 days

n=135 ⬇ N=353 ⬇ N=636 ⬇

Frequency of Cardiac Implantable Electronic Device Infections Among Antibacterial Envelope Recipients and Controls in the Entire Study Cohort and in the Propensity Score-Matched Cohorts

	TYRX™-A	TYRX™	Controls	P-Value*
Entire study cohort (N = 1,124)	0	1 (0.3%)	20 (3.1%)	0.001

*P-values from Fisher's exact test. Propensity-matched cohort 1 includes TYRX™-A and TYRX™ recipients and matching controls. Propensity-matched cohort 2 includes TYRX™-A recipients and matching controls.

Shariff et al_J Cardiovasc Electrophysiol 2015;26:783-9

TYRX as standard of care

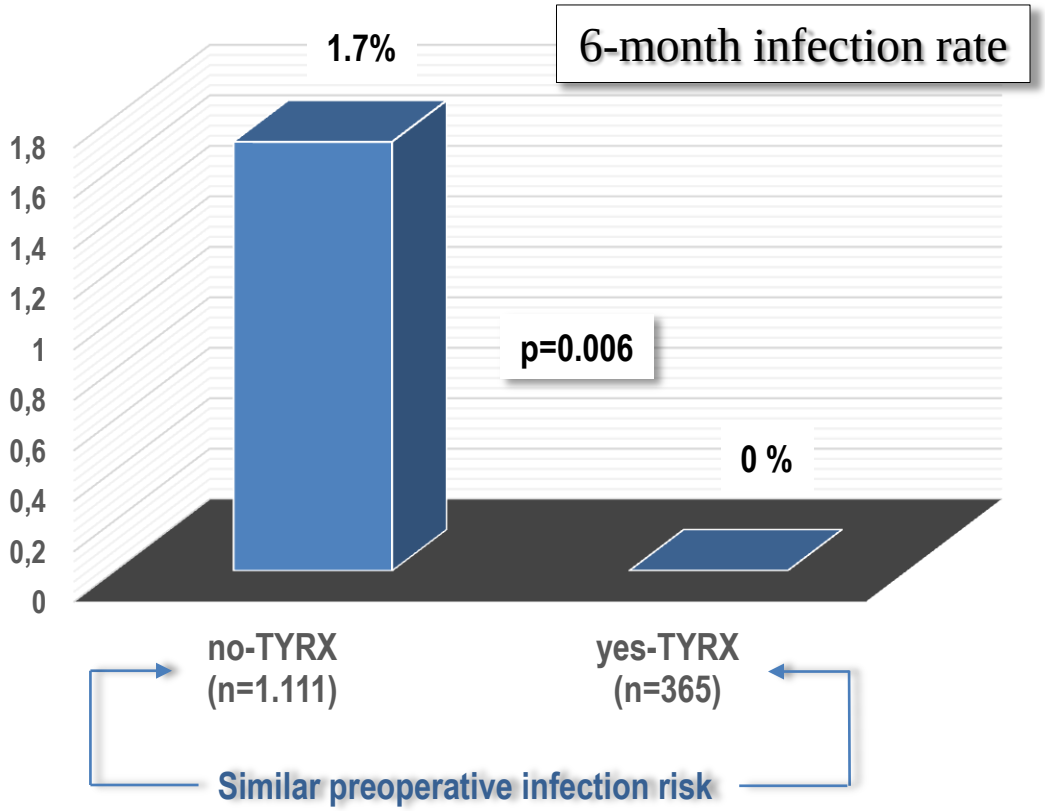
Single centre retrospective analysis of 1.476 pts who underwent CIED implantation; during the study (2011-2015) some implanters used the TYRX as a *standard of care*

Risk Score

- **Each factor was assigned of 1 point**

1. Diabetes mellitus
2. Heart failure
3. Oral anticoagulation
4. Chronic corticosteroid use
5. Renal insufficiency or failure
6. Prior CIED infection
7. Leads > 2
8. Epicardial lead(s)
9. Temporary pacemaker at implantation
10. Generator replacement or upgrade

- **Early reintervention (within 1 month)**



Shariff et al_J Cardiovasc Electrophysiol 2015;26:783-9

University of Pittsburgh score

Financial implications

TABLE 4

Financial Implications of Use of AIGISRx as a Standard of Care

	N	Infection Rate (N)	Infection Care Cost	Differential Cost*
All patients	365	1.71% (6.20)	$342,854	$23,863

Regione Emilia-Romagna

Direzione Generale Cura della persona, Salute e Welfare

Commissione Regionale Dispositivi medici
(DGR n. 1523/2008; Determina n. 14363/2016)

Scheda di Valutazione del dispositivo medico

TYRX™
INVOLUCRO ANTIBATTERICO RIASSORBIBILE

Documento CRDM n.3_2016
Settembre 2016

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Viale Pierluigi (Medico Infettivologo - AOU Bologna)

Risk score per pazienti candidati ad impianto/sostituzione/upgrade di ICD, CRT-D, CRT-P

Regione Emilia-Romagna

Allegato 1 - SCHEDA IMPIANTO e FOLLOW UP DISPOSITIVO TYRX

Centro:
- ❒Azienda Ospedaliera-Universitaria di Bologna
- ❒Azienda Ospedaliera-Universitaria di Ferrara
- ❒Azienda Ospedaliera-Universitaria di Modena
- ❒Azienda Usl di Ferrara
- ❒Azienda Usl della Romagna

Medico elettrofisiologo di riferimento: _____

Paziente: COGNOME _____ NOME _____

Data di nascita: _____/_____/_____ **Sesso**: □ M □ F

Data Intervento: _____/_____/_____ **Numero Scheda Dimissione Ospedaliera**: _____

Ricovero
- ❒ Ordinario
- ❒Day Hospital

Procedura
- ❒ 1° Impianto
- ❒ 1^Sostituzione
- ❒ Sostituzione successiva
- ❒ Reimpianto Controlaterale
- ❒ Upgrading

Tipologia CIED
- ❒ICD
- ❒CRTD
- ❒CRTP

FATTORI DI RISCHIO	Odds Ratio	*Barrare*
Reintervento precoce (entro 2 mesi da impianto)	15.04	❒
CRT-D/CRT-P vs ICD	7.57	❒
Almeno 2 elettrodi abbandonati	5.41	❒
Sostituzione device /revisione	3.67	❒
Pace maker temporaneo in atto	2.46	❒
FARMACI PAZIENTE		❒
Corticosteroidi (tp cronica)	13.90	❒
Anticoagulanti orali (tp cronica)	2.82	❒
CARATTERISTICHE PAZIENTE		❒
Insufficienza Renale in Dialisi*	13.39	❒
Disfunzione Renale Severa (eGFR < 30 ml/min)*	11.97	❒
Disfunzione Renale Moderata (eGFR 30-59 ml/min)*	5.46	❒
Diabete in trattamento farmacologico	3.50	❒
Scompenso cardiaco NYHA ≥3	2.57	❒
Genere Maschile	2.23	❒
ODDS CUMULATIVO di rischio infettivo		|__|__|

*I fattori di rischio relativi a: insufficienza renale in dialisi, disfunzione renale severa e disfunzione renale moderata devono considerarsi mutuamente esclusivi.

Tipo di infezione (nei 12 mesi successivi all'impianto):
- ❒ Infezione superficiale (cellulite regione della tasca con deiescenza della ferita, erosione o drenaggio purulento)
- ❒ Infezione profonda della ferita o della tasca
- ❒ Batteriemia persistente
- ❒ Endocardite

Data di insorgenza dell'infezione: |__|__|/|__|__|/|__|__|__|__|

Microrganismi isolati:

1._____Materiale_____
2._____Materiale_____
3._____Materiale_____

Worldwide Randomized Antibiotic EnveloPe Infection PrevenTion Trial (WRAP-IT)

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Background Cardiac implantable electronic device (CIED) infection is a major complication that is associated with significant morbidity and mortality. The aim of this study is to determine whether Medtronic TYRX absorbable envelope reduces the risk of CIED infection through 12 months of follow-up post procedure.

Methods WRAP-IT is a randomized, prospective, multi center, international, single-blinded study. Up to 7,764 subjects who are undergoing CIED generator replacement, upgrade, or revision, or a de novo CRT-D implant, will be enrolled and randomized (1:1) to receive the TYRX envelope or not. The primary endpoint is major CIED infection throughout 12 months of follow up after the procedure. Data will be analyzed with an intention to treat approach. WRAP-IT will also assess the performance of Medtronic's lead monitoring algorithms in subjects whose CIED includes a transvenous right ventricular defibrillation system.

Conclusions WRAP-IT is a large randomized clinical trial that will assess the efficacy of TYRX absorbable envelope in reducing CIED infection, define its cost effectiveness, and will also provide a unique opportunity to better understand the pathophysiology and risk factors for CIED infection. (Am Heart J 2016;180:12-21.)

Background

Over the last few decades, there has been growing evidence of the importance of Cardiac Implantable Electronic Devices (CIEDs) in improving both quality of life and survival among patients with heart disease.[1-4] With growing indications for CIED implantation, the incidence of these procedures continues to increase as the population ages and the density of comorbidities rises.[5-7] In addition, patients with CIEDs are undergoing several device-related procedures due to battery depletion, evolving indications requiring upgrades, and device or lead advisories and recalls.[8-10] This surge in CIED procedures has led to rising awareness of associated complications including CIED infections and lead complications. Many recent studies have indicated that the rate of newly diagnosed CIED infection is rising out of proportion to the rate of newly implanted devices,[7,11,12] and a large body of evidence from both tertiary centers and national databases has indicated that CIED infection is associated with significant morbidity and mortality, and represents a major financial burden.[7,13-20] The precise incidence of CIED infection is dependent upon the duration of follow-up, poorly characterized by the literature and lacks a prospective trial validation.

Improving strategies to reduce infection will be largely dependent on understanding the contributing factors to CIED infections. Currently, there are a number of risk factors that have been associated with infection that can be categorized as either procedure or patient related. The most frequently cited procedure related risks include device type, foregoing the use of IV prophylaxis, early reintervention (typically to manage a pocket hematomas and/or reposition or replace a lead), and most commonly secondary procedures for device replacements or upgrades.[21,22] A recent study demonstrated that CRT devices carried the highest risk for infection and that replacements increased the risk for all devices.[22] Patient characteristics commonly associated with CIED infection include, but are not limited to, diabetes, renal insufficiency, chronic steroid use, anticoagulation use, heart failure, previous open heart surgery.[23-25] To date, the use of

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RCT #NCT02277990

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