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The never-ending story of CIED infection prevention: shall we WRAP-IT and go ?

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Abstract.

CIED infection is perceived as substantial, ranging from 1-4% in literature depending on different studies and on the population profile, and can appear either as surgical-site or endovascular infection or both. Several factors have been found to be associated to CIED infection, that can be summarized as Patient-related (clinical profile, associated comorbidities, ongoing treatment as anticoagulants and immunosuppressants), Procedure-related (complexity of CIED surgery, type of surgery, previous pocket exploration) , and Center/Operator-related (centre/operator volume).

Thus, it is difficult to disentangle the extent of benefit that any intervention may offer to decrease this threatened complication, owing to its multifaceted complexity. The recently completed PADIT and WRAP-IT trials have significantly improved our knowledge in this field (nearly 20000 patients enrolled), reporting an infection rate of 1% to 1.2% in control-arm patients and a 20-67% infection decrease when incremental antibiotic prophylaxis is added on top of optimized preventative strategies. Observational registries

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highlighted that participation into a survey of CIED infection dramatically decrease infection rate by optimization of antisepsis protocols and operator awareness, that explains the low event rate observed in PADIT and WRAP-IT. While this consideration prompts each center to engage into a pro-active infection-prevention program, it makes a point in favor of antibiotic prophylaxis delivered locally ≥ 7 days, as enabled by TYRX in the WRAP-IT trial. However, care sustainability (the NNT in the most favorable WRAP-IT scenario is 100) suggests further analysis to understand the settings (Patient or Procedure related) most likely to benefit by such an enhanced prevention strategy.

Keywords: CIED infection; prevention; Antibiotic prophylaxis.

Background

Although perceived as a simple procedure, CIED surgery is a complex one, in that it dictates the permanence of prosthetic devices within the body indefinitely, and - unlike other surgical treatments - prosthetic materials are placed both intravascular and extravascular (1). The implication is that infection prevention strategies need to be targeted both at surgical site infection (SSI), where pacemakers and defibrillators are positioned, and at endovascular infection (EI) where intravascular leads dwell indefinitely (2, 3). It is conceivable that preventative strategies of SSI can also decrease EI to a certain extent, but for lead endocarditis stemming from an infection arising at sites other than the CIED pocket (4-7). In fact, recent evidence suggests that CIED infection without pocket involvement – not stemming out of an SSI - is associated with a worse prognosis (8, 9). CIED infection disproportionately increased in the past decade, raising concern about its deep-rooted causes, such as prevalence of in-hospital infections, change of in-hospital pathogens, and medical training (10-13). Pocket infection is prevalent among CIED infections (up to 69% of cases), mostly due to staphylococci species (10-12, 14), and prompts clinical efforts to prevent SSI (15). Based on the current clinical knowledge, CIED infections range from 1 to 4% being highest at replacements and upgrades (defined as addition of one or more lead/s) and according to specific patient profiles (13, 16-19). Pocket seeding by bacteria at the time of CIED surgery is the main mechanism of SSI (20); biofilm formation on the CIED/lead surface and at non-vascularized pocket tissue is the mechanism of escape to antibiotic activity, and of infection spreading to the circulation and to distant sites (1, 20-22). Incremental antibiotic prophylaxis conferred a non-significant reduction of CIED infection (from 1.03% to 0.78%) in the PADIT trial at the cost of exposure to multiple antibiotics (15). Thus, the concept of prolonged antibiotic prophylaxis at the pocket level (without systemic effects) until complete sealing of the surgical wound nested in our knowledge: a mesh eluting minocycline and rifampin at bactericidal concentration within 2 hours, that is maintained up to 7-14 days, was developed (23-24). Recent observational studies of locally-delivered minocycline and rifampin by such a knitted mesh containing the CIED proved a 70% reduction of CIED infection compared to historical cohorts, on top of pre-operative antisepsis, peri-operative sterility, and antibiotic i.v. prophylaxis (25-29). The randomized WRAP-IT study of the absorbable antibacterial envelope (TYRX) releasing minocycline and rifampin over the next 7 days (large size: 7.6 mg minocycline + 11.9 mg rifampin; medium size: 5.1 mg minocycline + 8.0 mg rifampin) as a means to prevent SSI was planned, and started enrollment in January 2015 (30).

The WRAP-IT trial: a milestone for infection prevention in CIED surgery.

The study engaged 776 implanting physicians from 181 centers in 25 countries worldwide, and randomized 6983 patients. Inclusion criteria were CIED replacement, upgrade, revision, and first CRTD implants; exclusion criteria were ongoing dyalisis, CIED infection within the previous 12 months, immunosuppression. Low-power (pacemaker+CRTP) devices accounted for 1722 (24.7%) procedures, first CRTD implants for 1122 (16.1%), and ICD/CRTD for 4131 (59.2%).

The first important contribution of the trial to our knowledge is a clear definition of CIED infection (Table 1). The primary endpoint measure, major CIED infection, was defined based on the sequel of CIED infection events (Table 1). The primary study endpoint was met: 25 (0.7%) patients had major CIED infections in the TYRX group compared to 42 (1.2%) in the control arm (40% relative risk reduction, p=0.041) at an NNT=200. Specifically, CIED pocket infection (SSI) was reduced by 61% (0.4% vs 1% in control arm). The effect on major CIED infection (37% reduction) was sustained in the 251 patients followed until 36 months. The success rate of TYRX implant was 99.7%, cross-over rate was low (0.7% control, 2.3% TYRX), and there was no safety issue related to the envelope. Consistent with literature (10-12), 64% of isolates in patients with infection were staphylococci species (30). Owing to the impact on pocket infection, 11 of 25 infections in the TYRX arm were EI: staphylococcus aureus was the causative agent in 6/8 isolates among these patients (1 pseudomonas, 1 enterococcus). However, the source of EIs was not investigated (i.v. lines ? other procedures ?). (30).

As reported in Table 2, the control arm infection rate varied, being highest for ICD/CRTD and lowest for first CRTD implants. In fact, there was no infection reduction in low-power CIEDs and first CRTD implants, although this was not a pre-specified sub-analysis. Major CIED infection indeed decreased by 67% (Table 2) in the ICD/CRTD replacement/upgrade subgroup, an effect comparable to that observed in a meta-analysis of previous observational studies (29). The NNT is 100 in this patient subgroup, that represented 59% of the study population.

What are the limitations of the WRAP-IT trial ?

Selection bias could be advocated, enrollment being non-consecutive, and TYRX commercial availability potentially excluding the highest risk candidates such as patients with a previous pocket entry for a non-infective reason, or with a specific risk profile (17, 26, 27). These concerns should be lifted by the multi-center PADIT trial, that reported a 1.54% infection rate in the CRT/upgrade/revision conventional arm, and by the DECODE observational registry (31) that reported a 1.2% infection rate in ICD/CRTD replacements/upgrades (59% of the WRAP-IT trial population). Both studies were based on all-consecutive patients across all manufacturers, and were completed before the availability of TYRX, thus excluding selection bias. In the DECODE registry (31), overall complications were doubled by upgrade (lead addition) that occurred in 18% of all-consecutive patients, and increased three-fold when hospitalization within the month prior to the procedure had occurred. This hints at a missing piece of information in the WRAP-IT trial: the number of patients undergoing CIED upgrade, and TYRX effect in this subgroup. In the REPLACE registry (32), upgrade was heavily burdened by complications compared to replacement without lead addition, infection being around

1.5%, as in the ICD/CRTD replacement/upgrade subgroup of the WRAP-IT control arm. Though hazard ratio varies widely across reports, upgrade doubles CIED infections on average, as in the literature review by Polyzos et al (17). Upgrade represents about 20% of ICD/CRTD surgery, thus this information is dearly awaited, to investigate whether TYRX benefit differs depending on procedure complexity (maximum benefit vs no benefit). The same concern arises with regard to previous pocket exploration for non-infective reasons (pocket revision, lead displacement, hematoma evacuation): all these settings have a 6-8 fold increased risk of infection (17). Specifically, the highest infection risk (15-fold increase) was observed in patients undergoing a repeated pocket entry in the 30-60 days following the index CIED procedure, that represented 1.6-2.3% of procedures in large studies (16, 18, 26, 27, 33). Would TYRX effect at SSI prevention be maintained in such a challenging setting? The only observation on very high risk patients (5.4% on steroids, 51% undergoing replacement or revision, 42% with > 2 intracardiac leads) reported a 5.4% infection rate (5/92 patients) in TYRX-treated patients, that compares favorably with the expected infection rate in this patients' subset (34). Indeed, Mittal et al. had previously reported a 6-months infection rate ranging from 4% (upgrade at low risk) to 33% (early system revision) in patients with a similar risk profile (26), that suggests a positive effect of TYRX in the selected high-risk population of the Hassoun observation (34). However, no controlled data are available in such patients, therefore subgroup analysis of upgrades and lead/pocket revision in the WRAP-IT trial might help to explore the extent of TYRX effect in these challenging scenarios.

How to put the WRAP-IT data in the broad context of CIED surgery today ?

Several retrospective registries (10, 13 , 16, 18, 19, 31-33) have tried to capture the infection rate across different populations of CIED recipients, yielding conflicting results that are mainly based on selection process (consecutive vs non-consecutive patients enrolment), patients profile (age and co-morbidities increased in the past 15 years), and procedure complexity (CRTD approaching 50% of high-power devices nowadays, underrepresented in the past). Overall, infection seems to range from 1 to 4%, being associated with patient-related factors (17, 34), procedure-related factors (16, 17, 18, 19, 32, 33), and center/operator volume (16, 35). Thus, the proportion of CRTD recipients, upgrades, CIED revision, patient profile, center characteristics makes comparison of different studies unreliable. Table 3 shows a limited number of studies enrolling patients in the decade 2005-2015. A key message by Ahsan et al (13) is that the implementation of a well-defined protocol for SSI prevention yielded a 53% infection reduction among skilled operators, meaning that compliance with good medical practice within a survey or registry aiming at detection of complications improves outcome. The prospective nature of a registry or a survey raises the awareness of the problem and increases compliance with the preventative strategy, as observed in the PADIT trial, where a trend to decreasing infections in both arms was observed during the study (15). A similar effect may be hypothesized by comparing the infection rate of the prospective DECODE registry (1.2%) to the retrospective studies by Ludwig et al (3.4%) and by Clémenty et al (2.3% in the ICD/CRTD cohort) in similar populations over 2010-2015 (18, 19, 31). Thus, it seems that physician training and compliance with a strict prevention protocol under a continued surveillance program may lower CIED infections at 1-1.2% nowadays (15, 30, 31). On top of this, the effect of a very keen approach based on incremental antibiotic prophylaxis (i.v. + local wash) guided by CIED infection bacteriology was

explored in the PADIT trial, demonstrating a 20% infection reduction in the broad scenario of CIED surgery, that did not reach statistical significance at an NNT=500.

What does the WRAP-IT trial add to the PADIT trial results ? The TYRX envelope ensures a bactericidal concentration of minocycline and rifampin that is maintained over the next 7-14 days, minimizing the risk of pocket seeding by bacteria that could eventually reactivate from a dormant biofilm at a later stage (20-22). Thus, the true advantage of topical antibiotic release vs PADIT strategy was a sustained bactericidal effect at no risk of systemic unwanted effects for a longer time. Consistent with this hypothesis are WRAP-IT results at 36 months, that stand on the achievement of a sterile pocket thanks to the envelope (23, 24). The reduction of infections in WRAP-IT was clinically and statistically meaningful with NNT=200, though low risk patients diluted the effect of the intervention (Table 2). When applied to ICD/CRTD "second surgery" only (replacement/upgrade accounted for 59% of patients), the NNT is 100 (Table 2), making TYRX efficiency more attractive. The design of WRAP-IT was more focused on "second CIED surgery" (replacement and upgrades accounted for 84% of patients), based on the background that surgery on first implants and on low-power devices has a limited risk, between 0.2 and 1% (13, 15-18, 30, 32, 33), a fact that was confirmed in the study (Table 2). In "second surgery" (replacement, upgrade, revision) the non-vascularized fibrotic capsule hinders antibiotic diffusion into the pocket and increases the chance of biofilm formation during CIED surgery, thus TYRX sustained activity in situ for > 7days is synergistic to i.v. prophylaxis, whose pharmacological deficiencies are fixed by minocycline and rifampin (21-24). However, the time of onset of bactericidal concentration and the interplay between bacteria load and host immune competence also play an important role in biofilm formation (21-24). Indeed, the 67% reduction in ICD/CRTD "second surgery" was the cornerstone of the WRAP-IT success (Table 2). CIED infection is strongly associated with repeated surgery, exceeding 15% at the 4th pocket entry in small series (36, 37). This thought should bring us back to the practice of CIED infection prevention at the "individual" level. Though TYRX effect was similar across subgroups (30), even an NNT=100 makes the widespread use of TYRX in high-power CIEDs not affordable, the current unmet need being the target most likely to benefit.

The "Goldilocks principle" in CIED infection is a risk of SSI substantial enough to benefit by a prolonged bactericidal prophylaxis in the pocket until complete wound sealing. How can we detect patients at residual risk despite optimal clinical practice + i.v. antibiotics ? Clinical sense argues against patients' allocation to a risk level by a single iconic tract (high-power/low-power, first surgery/second surgery) or by a complex risk score stemming from different studies yielding uncomplete predictors' concordance or different hazard ratios (risk of unreliability). Awaiting WRAP-IT sub-analyses, we should probably refer to factors known to increase SSI (Table 4) to maximize our efforts at infection prevention. On the contrary, risk factors promoting bacteremia as the leading infective cause (temporary pacemaker, indwelling venous catheters, peritoneal dialysis, fever) imply minimal /no benefit by TYRX owing to the different pathophysiology of CIED infection (endovascular rather than pocket infection). Though ICD and CRTD bulkier size dictate more extensive surgery, hence increased SSI risk (10, 16-18, 38), the severity of associated conditions (Table 4) or their clustering in an individual patient may contribute at a similar risk level beyond device size (17). Therefore, a comprehensive

patient evaluation shall offer the best guidance to tailor i.v. antibiotics and TYRX use. The time is not ripe to wrap high-power devices at replacement and go, we probably need to drill into the WRAP-IT data to unravel the truly highest risk subgroups.

How can we make proficient use of TYRX today ? In daily practice SSI risk appraisal stands on patients characteristics being detected *before* surgery (Table 4), and others that arise – less predictably - *during* surgery. The mixture of both should guide our decision "to WRAP-IT or not to WRAP-IT". My attitude today is to consider TYRX in the following:

- Early pocket re-entry (<60 days)
- Previous CIED pocket infection > 12 months
- Simultaneous lead extraction and re-implantation for non-infective reason
- Upgrade/replacement + any characteristic portending Vulnerability to SSI (Table 4)
- Complex Surgery (Table 4) lasting ≥ 4 hours (on top of i.v. re-bolus)
- Depressed Immune Response setting (Table 4)
- Uninterrupted dual-antiplatelet or anticoagulation + antiplatelet associated to Vulnerability to SSI (Table 4)

Prophylaxis in these scenarios have never been addressed by controlled studies as selected subgroups, and indeed they comprise the highest risk patients, which deserve all efforts at infection prevention. Taken all together, they sum up to about 20% of CIED recipients [10, 13, 15, 17, 18, 25-28, 31-33]. Some of these situations may be "too hot" for Goldilocks, as dialysis, chronic steroid treatment, CIED infection < 12 months, and any ongoing infective process were exclusion criteria in the WRAP-IT trial, whereas all the others were permitted.

Economic implications of TYRX use.

The pioneering observational studies of the antibiotic envelope (25-28) fostered an easy sustainability of TYRX use, that rested on a > 90% infection reduction with an infection rate between 1.8 and 1.9% in propensity matched cohorts (27, 28). At an estimated average cost of $47,885 - $54,926 per patient treatment, the savings stemming from infection prevention would allow TYRX use as standard of care (28, 39). Participation in a surveillance program (clinical trial, registry) leads to optimization of performance owing to awareness and compliance with a comprehensive preventative strategy, as unveiled by the randomized PADIT and WRAP-IT trials (15-30) and by observational registries (13, 31, 32). The true benefit of TYRX, estimated around 70% SSI prevention, denies sustainability as standard of care when a 1-1.2% infection rate is to be addressed. Further analysis of infection management in WRAP-IT will help to elucidate this aspect.

"Heard melodies are sweet

But those unheard are sweeter"

John Keats, *Ode on a Grecian Urn*

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Table 1. Definition of endpoints in the WRAP-IT trial [30]

CIED infection	Major CIED infection
Superficial cellulitis with wound dehiscence, erosion, or purulent drainage	CIED system removal
Deep incisional or generator pocket infection	Any invasive procedure without system removal
Persistent Bacteremia	Extended antibiotic therapy when the patient was not a candidate for system removal
Endocarditis	Death

CIED = Cardiac Implantable Electronic Device.

Table 2. Patients experiencing Major CIED infection [30].

	Control Group (3485)	TYRX group (3490)
Low Power	7/866 (0.8%)	7/856 (0.8%)
First CRTD implants	3/586 (0.5%)	7/536 (1.3%)
ICD/CRTD replacement-upgrade-revision	32/2033 (1.57%)	11/2098 (0.52%)

CIED = Cardiac Implantable Electronic Device; CRTD= Cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator.

Table 3. Infection rate in retrospective and prospective studies.

Study	Enrolment period	Study type	TYRX use	Patients	CIED Type	Procedure	FU time	Infection Rate
Ludwig (19)	2010-2013	retrospective	NO	4699	ICD/CRTD	ALL	12 months	3.4%
Clementy (18)	2012	retrospective	NO	9465	ICD/CRTD	ALL	12 months	2.3%
Replace (32)	2007-2008	prospective	NO	1744	ALL	ALL	6 months	1.3%

Ahsan (13)	2004-2009	retrospective	NO	1798	ALL	ALL	12 months	1.33%
		prospective	NO	981				0.62%
Kolek (27)	2005-2010	retrospective	NO	636	ALL	ALL	300 days	3.1%
	2009-2014	prospective	YES	488				0.2%
PADIT (15)	2013-2016	prospective	NO	12826	ALL	ALL	12 months	1.03% conventional antibiotic
								0.78% incremental antibiotic
DECODE (31)	2013-2015	prospective	NO	983	ICD/CRTD	ALL	12 months	1.2%

CIED = Cardiac Implantable Electronic Device; CRTD= Cardiac resynchronization therapy defibrillator; ICD = implantable cardioverter-defibrillator.

Table 4. Factors determining a greater SSI risk during CIED surgery [10, 13, 15, 17, 18, 25-28, 31-33].

Setting	Individual characteristics	Considerations
Early pocket re-entry (<60 days)	Lead dislodgement Hematoma Pocket revision	Individualized i.v. antibiotics: methicillin resistance frequent
Depressed Immune	Chronic inflammatory diseases on	Individualized

Defense	steroids Oncologic disease treated < 6 months Chronic infective process End-stage renal disease / Dialysis	i.v. antibiotics.
Vulnerability to SSI	Hospitalization within 30 days Index hospitalization longer than 7 days Previous CIED infection Chronic skin disease Pending skin issue by inside-out pressure	Individualized i.v. antibiotics: methicillin resistance frequent
Complex procedures	Lead extraction and re-implantation Upgrade (one or more lead addition) Multiple (> 3) pocket entries	Pocket exposure to bacterial seeding

CIED = Cardiac Implantable Electronic Device; SSI = surgical site infection.