Antibacterial envelope

for the prevention of cardiac implantable electronic device-related infections

Technology Guidance from the MOH Medical Technology Advisory Committee (MTAC)

Guidance Recommendations

The Ministry of Health's MTAC has recommended subsidy for antibacterial envelope for the prevention of cardiac implantable electronic device (CIED)-related infections in

- ✓ Patients deemed to be at high risk of CIED-related infections based on:
  - Patient-related risk factors such as end-stage renal disease, corticosteroid use, renal failure, history of device infection, chronic obstructive pulmonary disease (COPD), >New York Heart Association (NYHA) class II heart failure, malignancy, diabetes mellitus, fever prior to implantation, skin disorders, heparin bridging, and oral anticoagulants; OR
  - Procedure-related risk factors such as device replacement, revision or upgrade, generator replacement, and lead repositioning; OR
  - Device-related risk factors such as use of implantable cardioverter defibrillators (ICD), cardiac resynchronisation therapy - defibrillators (CRT-D), epicardial leads, abdominal pockets, and ≥2 leads.

- ✓ Patients receiving permanent pacemakers and cardiac resynchronisation therapy – pacemakers (CRT-P) if they have other high-risk factors for CIED infection.

Subsidy status

Antibacterial envelope is recommended for inclusion in the Medical Technology Subsidy List (MTSL) for the abovementioned indication(s) only.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 The MOH MTAC ("the Committee") considered evidence presented for the technology evaluation of antibacterial envelope for the prevention of CIED-related infections. The evaluation was conducted in consultation with clinical experts from the public healthcare institutions. Available clinical and economic evidence for antibacterial envelope was considered in line with the registered indication.

1.2 The evidence was used to inform the Committee's deliberations around five core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Overall benefit of the technology to the patient and/or the system;
- Cost-effectiveness (value for money), which covers the incremental benefit and cost of the technology compared to existing alternatives;
- Estimated annual technology cost and the number of patients likely to benefit from the technology;
- Organisational feasibility, which covers the potential impact of adopting technology, especially barriers for diffusion.

1.3 Additional considerations, such as ethical or social issues related to adoption of the technology, may also inform the Committee's deliberations.

Clinical need

2.1 CIED-related infections, whether pocket or systemic, can lead to CIED removal and antibiotics treatment, and are associated with significant morbidity, mortality, and healthcare utilisation. Despite the use of standard of care infection prevention practices such as prophylactic intravenous pre-operative antibiotics and advocacy of best surgical practices, CIED-related infections can still happen.

2.2 The Committee agreed that standard of care infection prevention techniques during CIED implantation is an appropriate comparator to adjunctive use of an antibacterial envelope with standard of care to prevent CIED-related infections. The antibacterial envelope is a single-use, fully absorbable microfilament mesh pouch that holds and is implanted together with the CIED to elute broad-spectrum antibiotics into the local tissue to prevent CIED-related infections.

Clinical effectiveness and safety

3.1 The Committee noted that the evidence was based on two systematic reviews and meta-analyses published in 2020, and two publications on WRAP-IT randomised controlled trial (RCT) with follow-up period of up to 36 months.

3.2 For safety, the Committee noted that there was no statistically significant difference in procedure- or system-related complications between patients who received an adjunctive antibacterial envelope with standard of care and standard of care alone at up to 36 months follow-up. There were no reports of allergic reactions to the envelope up to 36 months.

3.3 For clinical effectiveness, the Committee noted that:

- Patients who received an adjunctive antibacterial envelope with standard of care had a significantly lower risk of major CIED-related infections compared with patients who received standard of care alone at up to 36 months. This was driven mainly by significant reductions in localised major pocket infection rates. When stratified by risk of infection, significant reduction in major infection rates was only shown in studies that enrolled patients at higher risks for CIED-related infections, but not in those that included patients at any risk for CIED-related infection. Reported risk factors for CIED related infections were varied.
- Other risk factors identified including chronic renal disease or diabetes mellitus, and type of CIED device could influence the risk of CIED infection. In patients on a high-powered device like an ICD or CRT-D, the use of adjunctive antibacterial envelope and standard of care reduced the risk of major CIED infections by 50% (95% CI 0.29 to 0.90) to 90% (95% CI NR), with absolute reductions reported from 1.4%-2.2% to 0.2%-0.7%, when compared to standard of care alone.
- There was no statistically significant difference in overall incidence of mortality and systemic infections such as endocarditis and bacteraemia between adjunctive antibacterial envelope with standard of care and standard of care alone.

3.4 The Committee noted that the clinical evidence was limited by a lack of standardisation across studies in defining patients at high-risk for CIED infection, and the exclusion of certain high-risk groups (e.g. patients on dialysis) in some studies.

Cost-effectiveness

4.1 The Committee considered the published cost-effectiveness evidence of antibacterial envelope for the prevention of CIED-related infections based mainly on two cost-effectiveness analyses (CEA) from the USA and Canada, comparing

adjunctive antibacterial envelope with standard of care to standard of care alone in patients with risk of infections.

4.2 The Committee noted that the two studies reported a wide range of incremental cost-effectiveness ratios (ICERs). The wide varying ICERs reflected the uncertainty on the cost-effectiveness of antibacterial envelope in patients with risk of infections, possibly due to differences in baseline infection rates associated with standard of care applied, prior CIED infection and costs.

4.3 The Committee noted that the ICERs were sensitive to infection rates associated with standard of care and post-infection mortality. A low infection rate for standard of care of <1% generally favours standard of care, whereas adjunctive antibacterial envelope can be cost-saving if the infection rate for standard of care is high (e.g., ≥4% or 6%). As preprocedural comorbidities and intensity of CIED procedures can affect the standard of care infection rate, sub-group analyses from the CEA from USA found that factors associated with lower ICERs of less than US$33K per QALY gained were prior CIED infection, history of being immunocompromised, implantation of high-powered devices with ≥2 prior procedures, and revision or upgrade of low-powered devices. For these sub-groups, the CEA from USA had applied infection rates associated with standard of care ranging from 2.4% to 5.8%.

4.4 The Committee agreed that the antibacterial envelope may have a potential role in preventing CIED-related infections in special cases where various risk factors are identified, particularly concerning CIED infection rates, type of device required, post-infection survival outcomes, and costs associated with CIED infection in Singapore.

Estimated annual technology cost

5.1 Based on the projection of approximately 173 people in Singapore who would benefit from government subsidy for antibacterial envelope, the Committee estimated that the annual cost of providing antibacterial envelope was <$1 million.

Additional considerations

6.1 The Committee noted that the ACE-negotiated price for antibacterial envelope was comparable to overseas prices.

Recommendation

7.1 Based on the evidence of acceptable safety, clinical and cost-effectiveness in some high-risk populations, the Committee recommended subsidy for antibacterial envelope for the prevention of CIED-related infections in:

- ✓ Patients deemed to be at high risk of CIED-related infections based on:
  - Patient-related risk factors such as end-stage renal disease, corticosteroid use, renal failure, history of device infection, COPD, >NYHA class II heart failure, malignancy, diabetes mellitus, fever prior to implantation, skin disorders, heparin bridging, and oral anticoagulants; OR
  - Procedure-related risk factors such as device replacement, revision or upgrade, generator replacement, and lead repositioning; OR
  - Device-related risk factors such as use of ICD, CRT-D, epicardial leads, abdominal pockets, and ≥2 leads.

- ✓ Patients receiving permanent pacemakers and CRT-P if they have other high-risk factors for CIED infection.

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Medical Technology Advisory Committee as at 17 March 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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