A Cost Minimisation Analysis Comparing Oral Linezolid and Intravenous Daptomycin Administered via an Outpatient Parenteral Antibiotic Therapy Programme in Patients Requiring Prolonged Antibiotic Courses

Introduction

1.1 Background

Outpatient parenteral antibiotic therapy (OPAT) has become established as a safe and effective means of administering intravenous (IV) antibiotics in the last two decades [1], [2]. OPAT is commonly administered, with an estimated one in 1,000 people in the United States receiving the treatment annually [3]. Multiple studies have also demonstrated its considerable cost-saving potential in comparison with conventional inpatient-administered IV antibiotics [4]–[6]. However there has been a number of clinical studies published in recent years which indicate that for many infections traditionally treated with prolonged course of IV antibiotics, oral therapy may be substituted safely for part or all of the treatment course [7]–[15]. Although much literature exists comparing the cost of OPAT to conventional inpatient therapy, there is a paucity of literature comparing cost of OPAT with oral antibiotics in patients undergoing prolonged treatment courses in whom conversion to oral therapy would be appropriate.

1.2 Objectives

This study seeks to examine cost savings that may be accrued from usage of oral linezolid in place of IV daptomycin in patients requiring prolonged courses of antibiotic therapy in the Republic of Ireland. In order to do so we reviewed clinical guidance and evidence comparing the two agents in a range of infections to establish the clinical scenarios in which the agents would be interchangeable. We then sought to determine costs to the Irish healthcare system of each treatment approach using a decision tree model with probability inputs from the published literature and costing of the treatment scenarios.

1.3 Comparator treatments

Linezolid is a synthetic antibiotic belonging to the oxazolidinone class. It acts by inhibiting initiation of protein synthesis at the 50S ribosome. It is active against a wide-range of gram-positive aerobic bacteria,

some anaerobic bacteria, several mycobacterial species as well as nocardia [16]. First discovered in the mid-1990s, it was first approved for clinical use on April 18th 2000. When taken oral it has a bioavailability of nearly 100% and an extensive volume of distribution [17]. Its current licence allows it to be prescribed for a maximum of 28 days continuously after which the rates of adverse events increase. The main adverse effect leading to discontinuation when given for short courses is reversible myelosuppression [18]. With courses longer than 28 days, effects associated with mitochondrial toxicity such as peripheral neuropathy, hyperlactataemia and metabolic acidosis occur [19]. It has a clinically important drug interaction with serotonergic agents such as the commonly prescribed class of antidepressants selective serotonin reuptake inhibitors (SSRIs) which limits use in these patients [20]. It is not licensed for use in catheter-related BSI (CR-BSI) due to a small imbalance in mortality in an early open-label study of the drug [21]. Patent protection expired in 2015 leading to entry to the market of generic competitors and considerable reduction in price of linezolid.

Daptomycin is a cyclic lipopeptide antibiotic with a broad-spectrum of activity against gram-positive bacteria. It can only be administered intravenously (IV) and therefore if required in the community, can be administered via an outpatient parenteral antibiotic therapy (OPAT) programme. Adverse effects include muscle aches, rhabdomyolysis and eosinophilic pneumonitis [22]. As well as toxicities associated with the antibiotic itself, there are also a range of complications associated with administration of IV antibiotics. These include complications associated with peripherally inserted central catheter (PICC) line insertion such as bleeding and pneumothorax, as well as later complications including PICC line infection, secondary bloodstream infection (BSI), venous thrombosis and line occlusion [23].

Both antibiotics are widely used in the treatment of infections caused by resistant gram-positive bacteria such as methicillin-resistant staphylococci or vancomycin-resistant enterococci (VRE). Although data exists more widely to suggest that most microbiologically effective oral antibiotic therapies are comparable clinically to their intravenously administered equivalents, we felt these agents were most suitable for a cost minimisation analysis given linezolid's extremely broad spectrum of activity, its near

perfect bioavailability when taken orally and its place on treatment guidelines for common infections as a substitute for IV therapy [24], [25].

1.4 *Cost minimisation analysis*

Cost minimisation analysis was considered appropriate in this setting for a number of reasons. Our study used an extremely short time horizon as the endpoint was end of therapy rather than based on longer-term clinical outcomes given that in the infections compared, long-term outcomes were presumed to be the same. Despite the fact that IV therapy tends to be slightly worse from a quality-of-life viewpoint [26], we felt that over a two-week time horizon that the difference between cohorts from a quality-adjusted life year (QALY) point of view was likely to be minimal. Where cost effectiveness analysis has been used comparing IV to oral therapy in situations of clinical equivalence, there has been very minimal difference in clinical outcomes and QALYs between cohorts [26], [27].

Methods

2.1 Outcome measure

Total cost of care to the Irish healthcare system was the primary outcome measure in this study. The economic impact of switching eligible patients to oral linezolid was estimated by comparing treatment costs of OPAT daptomycin to those of oral linezolid for the final 14 days of an antimicrobial therapy course. A decision tree model was used in order to estimate costs of each treatment strategy and is outlined in more detail below.

2.2 Model Population

The base-case model population considered were admitted adult patients suitable for discharge from hospital with infections due to gram positive organisms requiring two further weeks of IV or highly bioavailable oral antibiotic therapy.

This cohort is generally being treated with a four- to six-week course of antibiotics. Therefore suitable patients would primarily be those with prosthetic and native bone and joint infections and those with BSIs with bacteria with appropriate susceptibility profiles in whom adequate source control has been achieved. However other infections requiring prolonged courses of antibiotics with suitable susceptibility profiles would also be suitable. Individuals in each population would need to have the oral route available for administration of therapy and no contraindications to treatment with either drug. This includes allergies or intolerances to either agent. In the case of linezolid this would also include co-prescription of serotonergic agents such as the commonly prescribed antidepressant class SSRIs.

There are certain disease areas in which daptomycin is used where linezolid is not licensed or where evidence for its use is lacking. These are catheter-related BSIs (CR-BSI), infective endocarditis and as initial therapy in *Staphylococcus aureus* BSI. Patients with *S. aureus* BSI in whom adequate source control has been achieved would be suitable for conversion to oral linezolid if they have completed two weeks of induction IV therapy.

2.3 Decision Tree Model

A two-week decision tree model captured both treatment pathways (Figure 1). A decision tree model was deemed suitable given these are acute care scenarios without any transmission dynamics. The endpoint for the model is the end of the antibiotic treatment course. Outcomes such as treatment failure and microbiological failure within the time horizon of the model were presumed to be equivalent given the evidence outlined below and so were excluded from the model. Clinical outcomes beyond the time horizon of the model were also presumed to be similar based on the clinical evidence and therefore costs beyond this were presumed to be equal. The model begins at the oral linezolid versus OPAT daptomycin decision node.

We used Microsoft Excel in order to tabulate and perform certain calculations on the data and used TreeAge Pro 2021, R1 (TreeAge Software, Williamstown, MA; software available at

http://www.treeage.com) in order to create and analyse decision trees as well as to conduct deterministic and probabilistic sensitivity analyses.

2.3.1 Model inputs

We utilised data from published literature to input values into the decision tree model. A breakdown of base-case probability estimates and references is presented in Table 1.

For a 14-day course of linezolid, we estimated incidence of adverse drug reactions (ADRs) leading to discontinuation from a review article assessing the safety profile of linezolid across a number of phase three studies encompassing 2,046 linezolid-treated patients [28]. We assumed that an equal amount of ADRs would occur in each week of treatment.

Complication rates with daptomycin use were taken from a study examining safety in 2,263 patients administered daptomycin and stratifying adverse events by duration of therapy [29]. Regarding the probability of PICC complications, we used data detailing the incidence of such complications per 1,000 line-days in patients receiving OPAT in the ambulatory setting [30]. We used the breakdown presented in this paper to estimate the likelihood of major and minor PICC complications.

2.3.2 Oral linezolid pathway

On the oral linezolid pathway, patients either finish therapy as planned or have an ADR leading to switch of therapy. If the ADR occurs in week one, patients are admitted and accrue the diagnostic-related group (DRG) cost of an admission related to drug toxicity [31] and were switched to intravenous daptomycin to complete their course on OPAT. If the ADR occurs in week two, the patient is admitted and accrued the drug toxicity DRG cost as well as the cost of completing therapy as an inpatient as it is unlikely OPAT would be organised and a patient discharged home in this timeframe. Alternative oral antibiotic options were not considered as appropriate therapeutic alternatives to oral linezolid for the purposes of this study and IV therapy was reinstituted on discontinuation of linezolid.

2.3.3 OPAT daptomycin pathway

On the OPAT daptomycin pathway, patients either completed therapy as planned or had a complication of therapy. We drew a distinction between PICC-related complications and ADRs. If a patient had an ADR to daptomycin, they accrued admission cost of a drug toxicity related admission and their therapy was switched to oral linezolid for the remainder of the treatment course. If the patient had a PICC-related complication, we then distinguished between minor and severe complications. Minor complications, such as occlusion or leak, accrued only the cost of replacement of PICC line without admission cost. Severe complications, such as infection or thrombosis, accrued the cost of replacement and short hospital admission using the appropriate DRG cost.

2.4 Costing

We estimated costs from the publicly funded health and social care system in Ireland perspective with all costs in 2021 euro. Therefore we included only direct costs to the health service. Indirect societal costs such as patient time travelling to and from hospital appointments, time being administered antibiotics in the community, and economic costs of missing work while on OPAT are likely to be substantial in societal terms but are not direct costs to the Irish health service. Given the time horizon was only two weeks, discounting was not a consideration. Costing was carried out in accordance with the Health Information and Quality Authority's (HIQA) Guidelines for the Economic Evaluation of Health Technologies in Ireland 2020 [32].

Costs were estimated insofar as possible by micro-costing methodology with some limited use of DRG data. In order for costing to reflect current practice and real world patients as much as possible, we collected limited patient data for the year 2020 of individuals who were discharged on OPAT daptomycin and maintained it on a password encrypted hard-drive and used this data to assist with certain aspects of our costing. We also used this data to assess savings that would have been accrued locally for the year of 2020. Data collected is presented in Table 2.

We attempted to be as meticulous as possible in calculation of all labour, hardware, pharmaceutical, logistical and miscellaneous costs. Where possible we obtained the actual costs of care from sources in the Health Services Executive (HSE) and for the remainder, we obtained costs from suppliers, the academic literature and used expert opinion. We followed HIQA guidance regarding the use of salary costs in economic analyses [32]. If cost data was obtained from a year other than 2021, the Central Statistics Office (CSO) consumer price index was used to convert costs 2021 euro [33]. Where costing data was sourced from a jurisdiction other than the Republic of Ireland, purchasing power parities were used to convert these costs [34] as is recommended by HIQA [32]. Costing breakdown is outlined in Table 3. Information was sought from a number of sources on the cost to the HSE of OPAT contracted to third party companies. Unfortunately this information is commercially sensitive and was not available to the authors.

2.4.1 Drug costing

The cost of generic linezolid in the Republic of Ireland was obtained from the HSE List of Prescribable High Tech Medicines February 2021 [35]. The price of the cheapest generic was selected for the purposes of this paper. Prices for daptomycin were obtained from the most recent entry for that agent in the Irish Pharmaceutical Healthcare Association (IPHA) price reduction document [36].

Linezolid dosage was standardised at 600 milligrams (mg) twice daily. This is the standard dosage for gram-positive bacterial infections. Daptomycin is available in vials of 350 mg and 500 mg. In order to calculate the most appropriate dosage of daptomycin for use in this study, we reviewed all patients discharged on OPAT daptomycin from our institution for the year 2020. We calculated the cost per dose for each patient and used the mean of these values as the cost per daptomycin dose for the base-case.

2.4.2 OPAT costing

Costs of OPAT for all patients included weekly medical and nursing review for the duration of time on OPAT as is international standard of care and current practice in our unit [37], [38]. It also included daily community nursing visits to administer the IV antibiotic. We used healthcare-administered OPAT (H-OPAT) in our base-case analysis as we found that only one out of 21 patients prescribed IV daptomycin via OPAT in 2020 was administered via self-administered OPAT (S-OPAT). We conducted a secondary analysis to assess costs in patients receiving S-OPAT. Community nursing time for those patients administered daptomycin via H-OPAT was calculated as 30 minutes. This varies on a patient-by-patient basis as in some instances IV daptomycin can be administered as a push rather than a 30 minute infusion, but given travel time associated with nursing staff travelling to a patient's home, this was felt to be conservative. We also factored in cost of transport of the antibiotics to the patients homes.

Costs of outpatient medical and nursing review were estimated using the relevant HSE pay scale [39] and incorporated guidance from HIQA on labour costs in economic analyses [32]. This entailed using the mean wage in the published payscale per unit time and adding on extra costs for pay-related social insurance, pensions and overhead costs. Outpatient medical reviews were calculated as 30-minute slots using the means of registrar rates and consultant rates for this time period. Nursing reviews were calculated as the mean clinical nurse specialist rate for a 30-minute period. 15 minutes of administrative staff time was included for each outpatient appointment. The cost of a full blood count, renal profile, liver profile and creatinine kinase levels were additionally included. For each patient discharged on OPAT, an hour-long initial nursing education consultation was included in the cost of OPAT as well as 30 minutes of nursing time per day of OPAT.

Costs of OPAT also included the cost of PICC line insertion by interventional radiology as is the practice in most hospitals in Ireland. Hardware costs for this procedure include the cost of the catheter itself, anchoring device and local anaesthetic drug costs. Staffing costs included 30 minutes of insertion time by an interventional radiology consultant or specialist registrar as well as 30 minutes of nursing time and 15 minutes of admin staff time. Staff costs of maintaining the catheters were included in the nursing time

allocated for outpatient appointments and for administration of antibiotics. Further expendable costs such as alcohol wipes, syringes and flushes were felt to be minimal enough as to not significantly impact costing.

2.4.3 Oral therapy costing

In addition to drug costs, one outpatient medical review during time on therapy was included for each patient. Similar to above, this was estimated as per HSE payscales incorporating HIQA guidance. A weekly full blood count was additionally included to monitor for myelosuppression as a potential toxicity of linezolid therapy. 15 minutes of phlebotomist time was also included as the patient would not have a PICC line.

2.5 Literature review

A literature search was conducted on PubMed and The Cochrane Library as well as a focused internet search. Studies were assessed comparing linezolid and daptomycin directly in a variety of infections including VRE BSI, methicillin-resistant *S. aureus* (MRSA) BSI, bone and joint infections and skin and soft tissue infections. We also reviewed guidelines for treatment of these infections. Where direct comparison data was lacking we highlighted certain reviews around usage of linezolid. In addition we highlighted certain recently published high-impact literature more broadly comparing intravenous antibiotic therapy to oral antibiotic therapy and comparison of bactericidal versus bacteriostatic agents.

Literature Review

3.1 Bloodstream infections

Given the limited available treatment options for VRE, much of the literature published directly comparing linezolid and daptomycin is in this disease area as both agents generally have activity against this pathogen. There have been four independent meta-analyses published in the last decade attempting to compare efficacy of the agents in the setting of VRE-BSI. All the reviews comment that the studies examined in each of the analyses were retrospective and relatively small scale and that prospective

randomised data in the area would be desirable. Zhao and colleagues reviewed 11 studies that compared standard or high-dose daptomycin (>6mg/kg) with linezolid and found similar efficacy and safety of the agents in treatment of VRE-BSI [40]. Chuang and colleagues examined 13 retrospective cohort studies and found that linezolid was associated with a significantly lower mortality for VRE-BSI [41]. Balli and colleagues similarly found a lower mortality in the linezolid-treated cohort [42]. Finally Whang et al found similar rates of microbiological cure between the agents with a trend towards improved survival in the linezolid group [43]. There was however a single relatively large retrospective cohort study of Veterans Affairs patients comparing the agents that found that treatment with linezolid was associated with a significantly higher risk of treatment failure and mortality when compared with daptomycin [44].

Regarding MRSA-BSI, Yeager and colleagues published a retrospective cohort of 215 patients examining outcomes of oral stepdown with linezolid compared to standard parenteral therapy with vancomycin or daptomycin. It was a heterogenous cohort including skin, bone and joint and endocarditis as well as other sources of BSI. The authors found no difference in 90-day infection-related readmission rate between the groups with a higher overall readmission rate in the standard parenteral therapy group, predominantly due to complications relating to vascular access [45].

There is unfortunately no well-conducted prospective evidence comparing the agents, however the available clinical evidence suggests that linezolid is at least as good as daptomycin in the treatment of these infections with a similar safety profile.

3.2 Bone and joint infections

The Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) study was published in 2019. Though not specific to these agents, it was a large and inclusive study that compared an IV antibiotic treatment strategy with a oral treatment strategy in a diverse group of patients with bone and joint infections. It included patients with prosthetic joint infections and was not restrictive in terms of

antimicrobial isolates. This trial found no difference between groups treated with IV or oral agents as a primary treatment strategy in this patient cohort [8].

The International Working Group on the Diabetic Foot (IWGDF) produced guidelines in 2019 advising on management of diabetic foot osteomyelitis [46]. Linezolid was recommended as an empiric antimicrobial option in patients at high risk for MRSA. They also recommend that mild-moderate diabetic foot infections that oral therapy can be instituted from the outset and that for osteomyelitis cases that initially require parenteral therapy, to switch to a high bioavailability oral regimen after five to seven days, if the likely or proven pathogens are susceptible and the patient has no contraindications to oral therapy.

Current Infectious Disease Society of America (IDSA) guidelines on prosthetic joint infection were published in 2012. They do not mention either daptomycin or linezolid as first-line treatment options for prosthetic joint infections. However for both methicillin-resistant and methicillin-susceptible staphylococci, as well as penicillin-resistant and susceptible enterococci, both agents are suggested as alternative treatment options. Linezolid is suggested at the 600mg twice-daily dosage, and it is specified that therapy may be oral or IV administered. Daptomycin is suggested at the 6mg/kg dosage [25].

The most recent IDSA guidelines on treatment of MRSA specifically recommend both agents as options in the treatment of skin and soft tissue infections, osteomyelitis and septic arthritis caused by MRSA [24].

In terms of clinical evidence, only one study was found comparing daptomycin and linezolid directly in this area. It was however a retrospective analysis with a small number of patients. Treatment strategies were heterogenous with both implant retention and removal strategies. The study nonetheless found that the agents were equivalent in terms of infection control rates. This particular study did however find that there were significantly fewer adverse events in those treated with daptomycin. However it should be

noted that patients in the linezolid group received up to 50 days of therapy which is considerably more than the licence allows for and the treatment course that we are considering in our analysis [47].

There are two independent systematic reviews addressing linezolid usage in prosthetic joint infection. The more recent published by Theil et al in 2020 examined 16 studies with a total of 372 patients [48]. Notably 46% of the infections were due to resistant coagulase negative staphylococci (CoNS) which accounted for a large proportion of infections in the local cohort of patients from whom we gathered data (Table 2). Treatment strategies consisted of both implant retention and removal. Overall infection control was achieved in 80%. The other review was published in 2014. There were a total of 293 patients in their analysis and they found cure rates of 79.9% overall, with 94% in patients whom the implant was removed and 69.9% in instances where it was retained [49]. Both analyses concluded that linezolid is a good treatment option for infections of this nature with cure rates comparable to better studied therapies.

3.3 Skin and soft tissue infections (SSTIs)

A recently published network meta-analysis compared four anti-MRSA agents (vancomycin, linezolid, tedizolid and daptomycin) in the treatment of MRSA-caused SSTIs. The authors included twenty eligible randomised controlled trials (RCTs) involving 7,804 patients. They concluded based on the evidence that ranking probabilities indicated that linezolid had the highest probability of being ranked best in terms of clinical and microbiological success [50]. There was no difference between any two antibiotics with regard to safety.

Again there is a paucity of data directly comparing the agents. However a systematic review looking at four studies comparing linezolid to vancomycin (regarded as standard of care) in MRSA SSTIs observed a trend towards greater effectiveness of linezolid [51]. A review article assessing the effectiveness of linezolid, tigecycline, daptomycin and vancomycin in complicated SSTIs caused by resistant gram positive organisms concluded that while none of the agents showed definite superiority over any other ‘linezolid offers by far the greatest number of patients included in controlled trials’ [52].

3.4 Bacteriostatic verus bactericidal

Much of the reticence regarding substitution of daptomycin with linezolid in spite of linezolid's broader spectrum concerns the bacteriostatic activity of linezolid as opposed to the bactericidal action of daptomycin. This concern is not backed up by clinical data. In a systematic review of 56 studies comparing bacteriostatic versus bactericidal antibiotic therapy, 'virtually all available data from high-quality, RCTs demonstrate no intrinsic superiority of bactericidal compared to bacteriostatic agents' [53].

3.5 Areas requiring further research

Linezolid is not yet established as a drug for the initial treatment of infective endocarditis. In most instances bactericidal action is preferred for agents undergoing trials in this condition [54]. There are several case series and reports of the agent being used successfully in endocarditis caused by resistant gram positive bacteria [55], [56], however there is insufficient data to support its use routinely. It was however one of the main therapies used a oral stepdown in a landmark study examining partial oral therapy for infective endocarditis [7], although in all instances was used in combination with another oral agent. Given additional complexities of calculating complication rates with another agent, we could not say definitively that findings from our study would be applicable in this scenario.

Linezolid is not licensed for treatment of CR-BSI. This is due to a mortality imbalance seen in an early study comparing the agent to vancomycin and oxacillin [21]. However this trend was not observed in those with gram-positive infections only. Nonetheless this cohort would not be considered as part of our model population.

Results

4.1 Base-case analysis

Results of the base-case analysis are presented in Table 2 with a rolled-back decision tree presented in Figure 2. Under the model base-case, the total cost of treatment with OPAT daptomycin was €3,496.84

and the total cost of treatment with oral linezolid was €772.01. Therefore the oral linezolid treatment strategy would be projected to save the Irish health service €2,724.83 per patient treated.

4.2 Deterministic Sensitivity analyses

We conducted a number of one-way deterministic sensitivity analyses in order to test the robustness of the base-case findings when certain parameters were altered. Results of the sensitivity analyses are presented in Table 4 and a tornado diagram is presented in Figure 3.

4.2.1 Daptomycin pricing

Daptomycin has steadily decreased in price over recent years. As well as this, pharmaceutical products are often subject to confidential pricing agreements between companies selling the drug and buyers. Therefore the true price paid for the drug may not be in the public domain. We therefore conducted a sensitivity analysis comparing base case results with those of a scenario in which daptomycin is priced at 50% of the listed price. In this scenario, the cost of the OPAT daptomycin strategy was reduced from €3,496.84 in the base case to €2,573.33. The resultant saving per patient treated with oral linezolid would be €1,801.32.

4.2.2 Linezolid ADR rate

We assessed the impact of a higher rate of ADRs with linezolid therapy. If the rate of ADRs on linezolid therapy is increased to twice the rate in the literature, the cost of linezolid therapy increases from €772.01 per patient treated to €845.73. This reduces the saving per patient to €2,651.11.

4.2.3 PICC complication rate

Finally, given the data on PICC complication rates in OPAT were imputed from a single centre study, we calculated the effect on the base case results with reduced complication rates. With a complication rate of 50% that of the base case, the cost of OPAT daptomycin is reduced only minimally to €3,477.05 with a resultant saving of €2,705.53 per patient in the linezolid arm.

4.3 Probabilistic sensitivity analysis

We conducted a probabilistic sensitivity analysis varying the uncertain parameters on our model. For all probabilities, we calculated the confidence intervals for each and used a beta distribution from which to select values. For any non-micro-costed or uncertain monetary values within our model, we varied the costs +/-20% as recommended by HIQA and used a gamma distribution from which to select values. We then conducted a Monte Carlo analysis with 10,000 simulations. Results are outlined in Table 5. The mean cost of the oral linezolid treatment strategy was €772.12 with a 95% confidence interval of €743.46 – €800.78. The mean of cost of OPAT daptomycin was €3,499.73 with a 95% confidence interval of €2,565.81 – €4,433.65. Oral linezolid was the cheaper strategy in 100% of simulations.

4.4 Post-hoc secondary analyses

4.4.1 Discharged population established on OPAT

We conducted a secondary analysis of the base case in a discharged population established on OPAT daptomycin with two weeks of therapy remaining. Costs for this population included drug costs, OPAT administration costs and weekly medical and nursing review as well as laboratory costs but did not include cost of delayed discharge, PICC line insertion or inpatient OPAT nurse review. In this scenario the total cost of treatment with OPAT daptomycin would be €2,499.96. Oral linezolid remains the cheaper for this population option with a saving of €1,727.84.

4.4.2 Self-administered outpatient antibiotic therapy (S-OPAT)

We decided to also conduct an analysis comparing costs of a patient who would be eligible for S-OPAT. In order to calculate this, we removed the cost of nurse visits for antibiotic administration and added an extra hour of nursing education time. This results in a cost of €3,226.13 for the OPAT daptomycin strategy with a saving of €2,454.12 in the base case

4.5 Applicability of findings locally

In an analysis of data locally, there were 21 patients discharged from our institution on OPAT IV daptomycin between 1st January 2020 and 31st December 2020.

Of these patients, eight (33.3%) were unsuitable for treatment with linezolid, four (19.0%) due to co-prescription of serotonergic medications, one due to documented intolerance to linezolid and two due to infection factors. A further one patient would have fit criteria but was co-prescribed IV ertapenem and so the cost-savings calculated would not have been applicable.

12 patients would have fit our criteria for stepdown therapy with oral linezolid. Of these, four would have been patients similar to the base-case with the remaining eight having been established on OPAT daptomycin and therefore would be akin to those examined in the secondary analysis. This would have resulted in an estimated cost-saving of €24,722.04 for the year of 2020 in our institution had the practice been instituted.

Discussion

5.1 IV and oral treatment strategies

Given the multitude of studies published on the relative efficacy of oral antibiotic therapy in certain infections as compared with traditional long-course IV antibiotics [6]–[14], this study highlights cost-savings that could potentially be realised if such evidence is heeded. We decided to only perform this analysis on patients switching from IV to oral therapy for the final 2 weeks, however much of the data suggests it is safe in certain infections to initiate oral therapy at the outset with likely resultant further reductions in inpatient and OPAT costs. We calculated cost for linezolid and daptomycin, but much of the cost for the IV treatment strategy was in the extra inpatient days, the logistics of providing the service in the community, central venous access insertion and complications and monitoring of such patients which would be applicable to any oral stepdown.

As well as the literature discussed above pertaining to this research, there are multiple studies currently underway further evaluating oral antibiotics for infections conventionally treated with IV such as gram-negative bacteraemia [58], [59] and *S. aureus* bacteraemia [60]. It is important in conjunction with this research for policymakers to have an understanding of the economic implications. If non-inferiority is demonstrated, in the right settings swift integration of such practice could benefit both patients from a quality-of-life viewpoint [26] and an economic one.

We would caution against extrapolating too widely the concept that oral antibiotic therapy is equivalent to IV therapy as this is not true in every setting and prolonged courses of IV therapy remain a necessary component of care in many infections.

5.2 OPAT and conventional inpatient care

It is worth noting that although more expensive than oral therapy as demonstrated by this analysis, OPAT has been proven to be a much less costly means of providing care than conventional inpatient administration of intravenous antibiotics [2], [61]. Indeed in our analysis, the cost of OPAT daptomycin would be far below the cost of providing inpatient care if calculated based on DRG costs (cost of 14 days of inpatient care would be equal to €7,786.10).

5.3 Limitations

There are a number of limitations to our analysis. Although the data comparing linezolid and daptomycin indicated that they were similarly effective with similar adverse event rates, the literature was heterogenous and there was a lack of high-quality prospective studies. This is an issue prevalent within literature comparing antibiotic agents.

Complication rates and probabilities for the decision tree model were derived from a number of different sources rather than a single well-conducted study. However all source material in this regard were large well-conducted studies with data specific to the clinical situation being addressed.

Decision tree models are also problematic in that they don't capture the inherent complexity of a real-life heterogenous group of patients and the infinite number of potential outcomes in a given clinical situation.

Costing is very challenging in the Irish healthcare context. Although all costing data was sought from the relevant sources, certain costs were commercially sensitive and subject to confidentiality agreements. For instance direct charges to the HSE from the contracted company that provides OPAT were unavailable and the process had to be micro-costed based on the components of care. Micro-costing also proved to be challenging with no clear template for doing this within the Irish health system. Although staffing costs were readily available, certain costs had to be sourced from non-HSE sources or from the academic literature.

Conclusion

Our study suggests that considerable savings could be accrued in patients suitable for conversion of IV daptomycin to oral linezolid. These findings were robust to multiple sensitivity analyses. Given the data emerging indicating safety of conversion from IV to oral therapy in an increasing number of clinical scenarios, further economic studies of this nature would be useful to characterise the extent of these savings.

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Declarations

Competing Interests Statement

The authors have no conflicts of interest to declare

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Author Contributions

Dr EF: Designed study, collected data, designed model, statistical analysis, drafted paper

Dr AJ: Advised regarding study design and clinical aspects, edited paper

Ethics approval

Ethics approval for this research was granted by the University College Cork Clinical Research Ethics Committee. Reference number: ECM 4 (g) 6/7/2021.

Branch in decision tree	Probability	Reference
Oral linezolid		
Adverse drug reaction	0.024	[28]
Finish therapy	1 – 0.024	Inferred
Adverse drug reaction week one	0.5 (0.024)	Expert opinion
Adverse drug reaction week two	0.5 (0.024)	Expert opinion
OPAT[a] daptomycin		
PICC[b]-related complication	0.053	[30]
Adverse drug reaction	0.015	[29]
Finish therapy	1 - (0.053+0.015)	Inferred
Minor PICC complication	0.83 (0.053)	[30]
Major PICC complication	0.17 (0.053)	[30]

Table 1: Breakdown of probabilities included in analysis

[a] Outpatient parenteral antibiotic therapy
[b] Peripherally inserted central catheter

Characteristic	Patients discharged on daptomycin	Patients suitable for linezolid
Total	21	13
Gender		
Male	13 (61.9)	7 (53.8)
Female	8 (38.1)	6 (42.9)
Linezolid Substitutable		
Yes	13 (61.9)	
No – total	8 (38.1)	
No – co-medications	4 (19.0)	
No – intolerance	1 (4.8)	
No – infection factors	2 (9.5)	
Co-prescribed Antimicrobials		
None	18 (85.7)	12 (92.3)
Ertapenem	2 (9.5)	1 (7.7)
Pipericillin-tazobactam	1 (4.8)	0 (0.0)
Infection		
Prosthetic joint infection	11 (52.4)	8 (61.5)
- Implant retained	5 (23.8)	4 (30.8)
- Implant removed	6 (28.6)	4 (30.8)
Other orthopaedic metal infection	1 (4.8)	1 (7.7)
Bloodstream infection	3 (14.3)	1 (7.7)
Infective endocarditis	2 (9.5)	0 (0.0)
Osteomyelitis	1 (4.8)	1 (7.7)
CNS[a] infection	1 (4.8)	1 (7.7)
Skin/soft tissue infection	1 (4.8)	1 (7.7)
Post-operative collections	1 (4.8)	0 (0.0)
Microbial isolates		
Monomicrobial	14 (66.7)	9 (69.2)
Polymicrobial	7 (33.3)	5 (38.5)
VRE[b]	3 (14.3)	2 (15.4)
Other enterococci	1 (4.8)	0 (0.0)
MSSA[c]	6 (28.6)	4 (30.8)
MRSA[d]	0 (0.0)	0 (0.0)
CoNS[e]	13 (61.9)	9 (69.2)
Streptococcal sp	2 (9.5)	2 (15.4)
Corynebacterium sp	1 (4.8)	1 (7.7)
Escheria coli	2 (9.5)	1 (7.7)
Klebsiella sp	1 (4.8)	1 (7.7)
Other GNB[f]	2 (9.5)	1 (7.7)
Clostridium perfringens	1 (4.8)	1 (7.7)
Candida sp	1 (4.8)	0 (0.0)

Table 2: Patient characteristics. Data are presented as n (% of total displayed at top of individual columns) unless otherwise stated

[a] Central Nervous system
[b] Vancomycin resistant enterococcus
[c] Methicillin susceptible *staphylococcus aureus*
[d] Methicillin resistant *staphylococcus aureus*
[e] Coagulase negative staphylococci
[f] Gram-negative bacilli

Item	Cost	Source
Drugs		
Linezolid packet of 10 600mg tablets	226.78	HSE[a]
Linezolid per day	45.36	HSE
Daptomycin 350mg vial	79.56	IPHA[b]
Daptomycin 500mg vial	117.41	IPHA
Staffing		
Consultant avg. hourly rate	110.61	HSE/HIQA[c]
Registrar avg. hourly rate	46.91	HSE/HIQA
Clinical nurse specialist avg. hourly rate	38.03	HSE/HIQA
Community nurse avg. hourly rate	29.69	HSE/HIQA
Administrative staff avg. hourly rate	22.50	HSE/HIQA
Laboratory scientist avg. hourly rate	31.53	HSE/HIQA
Laboratory		
Full blood count reagents	1.00	CUH[d]
Renal profile reagents	0.50	CUH
Liver profile reagents	0.50	CUH
C-reactive protein reagents	0.20	CUH
Creatinine kinase reagents	0.20	CUH
Staffing time daptomycin tests	7.87	CUH
Staffing time linezolid tests	3.93	CUH
PICC[e] line costs		
Catheter device and pack	276.20	Supplier/literature
Anchoring device	29.18	Supplier/literature
Instruments	20.35	Supplier/literature
Sedatives	3.03	Supplier/literature
Local anaesthetic	2.30	Supplier/literature
Insertion – staffing	64.05	HSE/Expert opinion
Community antibiotic administration		
Nursing costs – push	14.87	HSE/Expert opinion
Nursing costs – 30 minute infusion	29.74	HSE/Expert opinion
Cold chain costs per patient	100.00	Supplier
Diagnostic-related group Multi high per diem		
Prosthetic joint infection	497.00	HSE
Osteomyelitis	600.00	HSE
Skin and soft tissue infection	492.00	HSE
Infective endocarditis	721.00	HSE
Diagnostic-related group admission totals		
Toxic effect of drugs Minor	1,599.00	HSE
Sequelae of treatment Minor	2,165.00	HSE

Table 3: Breakdown of costs included in analysis (data are presented as n displayed in 2021 euro)

[a] Health Services Executive
[b] Irish Pharmaceutical Healthcare Association
[c] Health information and Quality Authority
[d] Cork University Hospital
[e] Peripherally inserted central catheter

Scenario	Oral Linezolid	OPAT[a] daptomycin	Cost saving
Base case	772.01	3,496.84	2,724.83
Sensitivity analyses			
Daptomycin 50% pricing	772.01	2,573.33	1,801.32
Increased linezolid ADR[b] rate	845.73	3,496.84	2,651.11
Decreased line-related adverse event rate	772.01	3,477.05	2,705.04
Post-hoc secondary analyses			
S-OPAT[c]	772.01	3,226.13	2,454.12
Discharged patient established on OPAT	772.01	2,499.96	1,727.95

Table 4: Results of base case, sensitivity analyses and post-hoc secondary analyses (data are presented as n displayed in 2021 euro)

[a] Outpatient parenteral antibiotic therapy
[b] Adverse drug reaction
[c] Self-administered outpatient antibiotic therapy

Statistic	Oral linezolid	OPAT[a] daptomycin
Mean	772.12	3499.73
95% confidence interval	743.46 – 800.78	2,565.81 – 4,433.65
Minimum	732.02	1832.24
Median	770.92	3470.94
Maximum	836.73	5522.51

Table 5: Results of probabilistic sensitivity analysis (data are presented as n displayed in 2021 euro)

[a] Outpatient parenteral antibiotic therapy

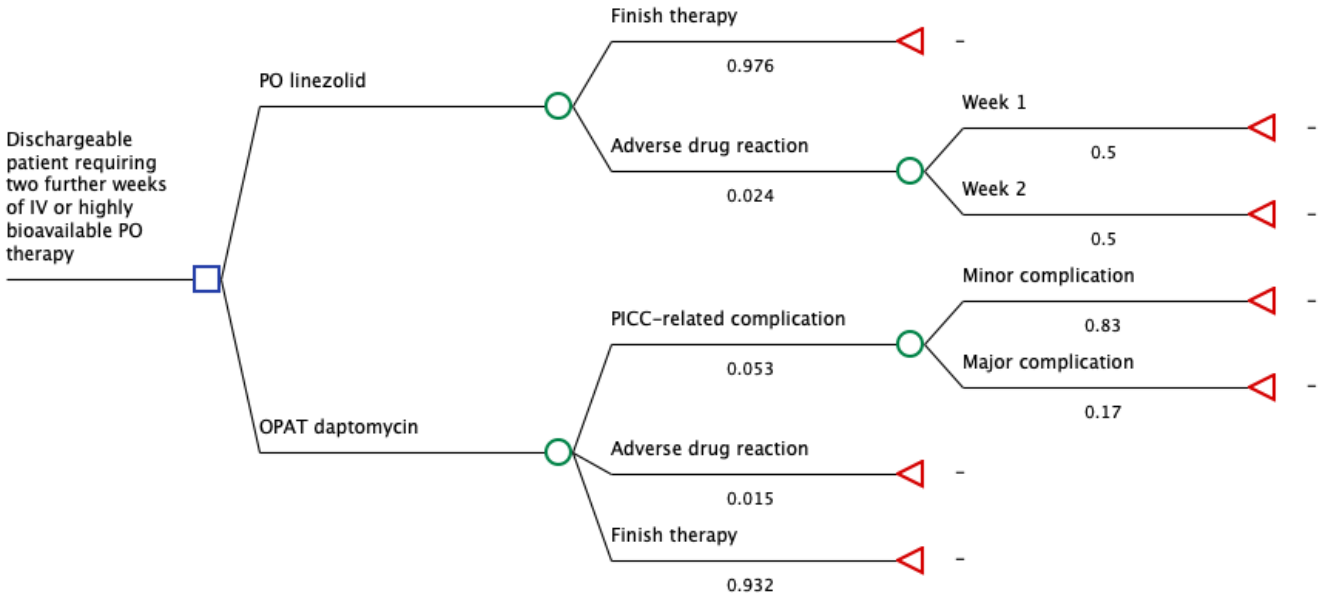

Figure 1: Decision tree model

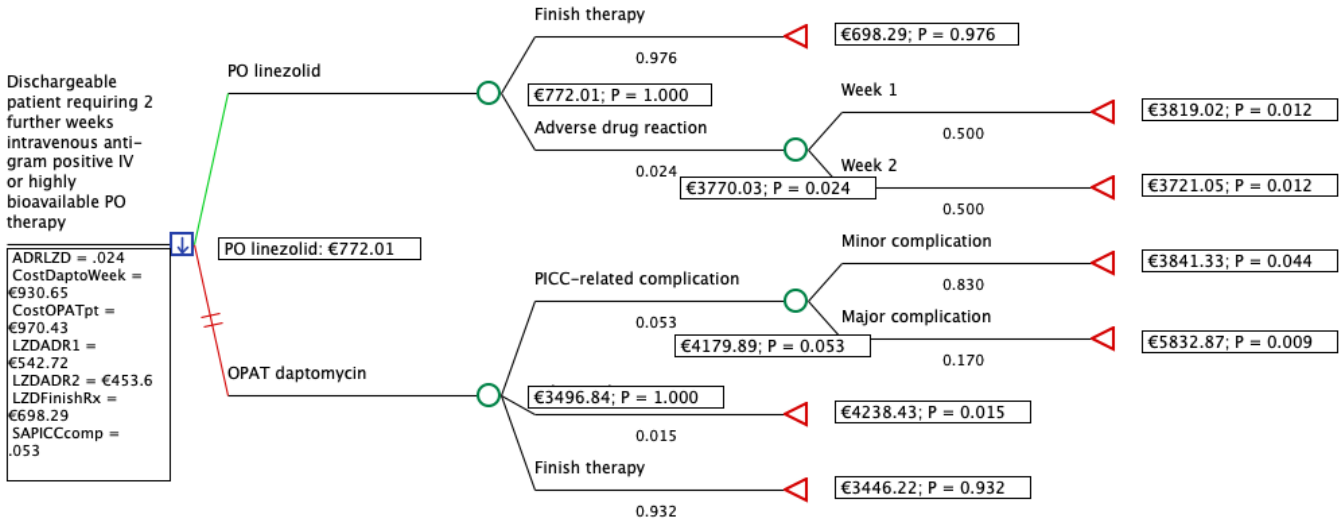

Figure 2: Decision tree model with base-case values rolled back

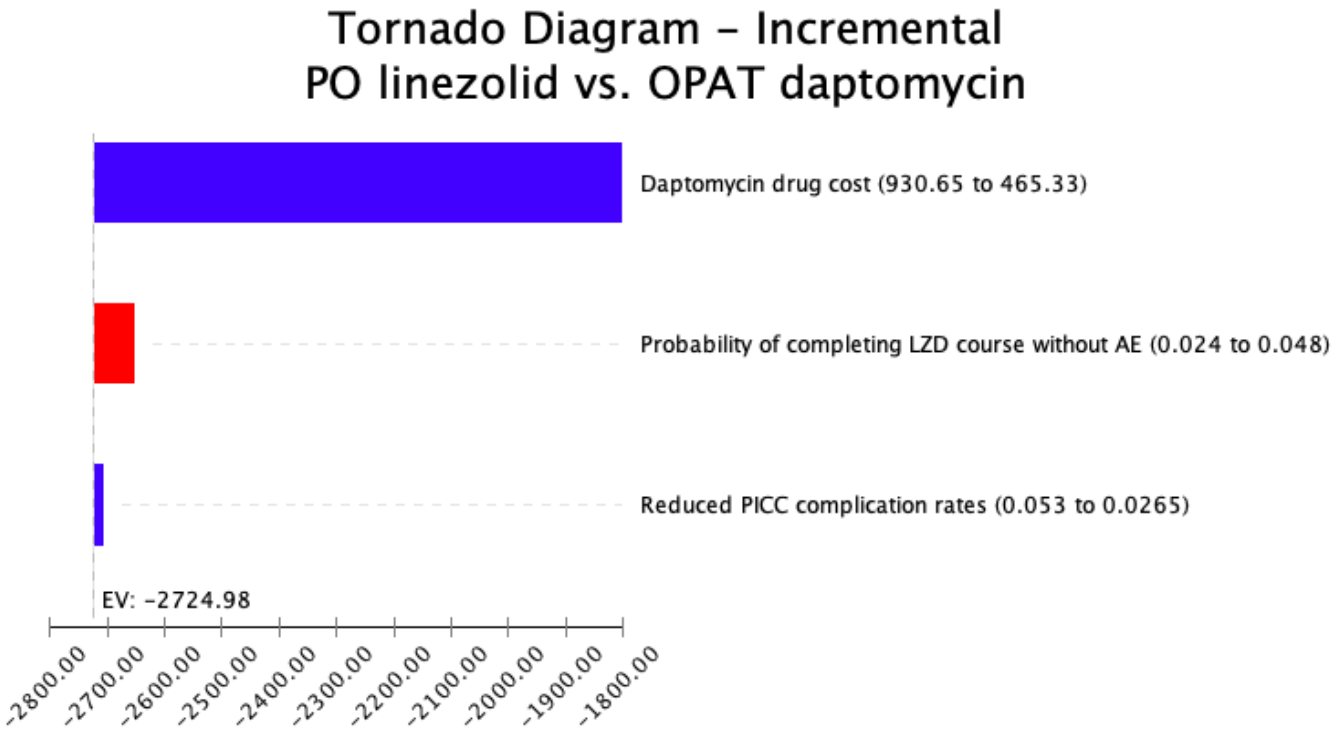

Figure 3: Tornado diagram of deterministic sensitivity analyses