

A REVIEW OF THE HEALTH ECONOMIC AND RESOURCE UTILIZATION LITERATURE FOR THE USE OF TIGECYCLINE TREATMENT OF COMPLICATED INTRA-ABDOMINAL INFECTIONS

Abstract

Objectives—Complicated intra-abdominal infections (cIAIs) infect deep soft tissues requiring surgical interventions and often result in decreased quality of life due to hospitalization. In addition to tigecycline, treatment of cIAI includes other drugs such as ceftriaxone, ciprofloxacin, imipenem, and levofloxacin. In this study, we conducted a literature review using publically-available databases focusing on the health economic and resource utilization estimates of tigecycline and the other agents as first-line treatment of cIAIs.

Methods—The databases used in this systematic review included PubMed and 42 unique HTA organizations. Search terms included “tigecycline” in combination with “Health Economics,” “Resource Utilization,” “Cost-Effectiveness,” and “Length of Stay.” The search criteria excluded articles with the following characteristics: without abstracts, published over 10 years ago, or not in English. Articles were then determined for eligibility using four additional inclusion criteria: 1) Indication, 2) Bacteria Type, 3) Qualitative Assessment, 4) Technicality. Studies were analyzed independently and not pooled because this was not a meta-analysis.

Results—After applying our filters to the search criteria, we identified 9 unique papers on the health economics and resource utilization of using tigecycline as first-line treatment of cIAIs. Though the health economic search resulted in only a few number papers on the cost-effectiveness of tigecycline, the messaging was consistent: tigecycline showed competitive clinical effectiveness and economic resource utilization versus several different comparators despite higher acquisition expenses. Several studies established that in terms of length of stay (LoS), total costs of hospitalization and other resource utilization parameters tigecycline was not inferior and thus the results do not favor one treatment over another.

Conclusion—The health economics literature estimates tigecycline to have comparable total cost per patient with respect to comparators. The broad spectrum activity of the drug avoids inappropriate treatments which are associated with increased resource utilization and result in higher costs. In view of the alarming spread in antibiotic resistance, the addition of another treatment option offers a valuable tool to counteract a mono-culture of therapies applied against cIAIs.

Introduction

The indiscriminate demand for antibiotics in non-emergency situations and their routine use in industrial food animal production have contributed to the public health crisis of human antibiotic resistance [1]. Amongst governmental agencies the US Centers for Disease Control and Prevention (CDC) has voiced concern about this dire state of affairs, raising the specter of a return to the pre-biotic age [2]. With the spread of antimicrobial-resistant (AMR) bacteria, the management of infectious diseases has become increasingly complex and difficult choices need to be made at the outset of each treatment regime which cumulatively have far-reaching consequences. For instance, the national cost of antibiotic resistance in the U.S. has been estimated by the CDC in 2011 at about \$US20 billion annually [3]. Moreover, the same issues affect healthcare worldwide prompting an ominous warning from World Health Organization [4].

In view of this state of affairs, there is an urgent need for a new generation of antibiotics. The acquisition of drug resistant microbes is particularly acute in health care setting. For this reason these issues are an important consideration during the treatment of complicated intra-abdominal infections (cIAIs) and the related complicated skin and skin structure infections (cSSSIs). A recent study in a teaching hospital located in Shanghai, China investigated the rise in resistance to carbapenems and found none of the 77 clinical isolates measured were susceptible to ertapenem while 6.5% and only 1.3% were susceptible to imipenem and meropenem, respectively. The study found that tigecycline and

colistin were very active against the resistant infections [5]. Tigecycline is a tetracycline class antibacterial which specifically targets a defense mechanism which imparts drug resistance [6,7]. It is indicated for patients 18 years or older in cSSSIs, cIAIs and community-acquired bacterial pneumonia. It was approved by the US Food and Drug Administration (FDA) for the former two in 2005, with indication for the latter following in 2009. The European Medicines Agency (EMA) issued a marketing authorization to tigecycline in 2006 for all of its indications. In particular, tigecycline [8] proved to be effective against a broad range of bacteria and it has been shown to be immune to easy mutations [9].

A review of the global health economic outcomes for the use of tigecycline in cIAI has not been undertaken. Current studies assess only costs, length of stay or efficacy outcomes for tigecycline in selected markets. This study aims to assess the global standing of tigecycline from a health economic perspective based on a review of the health economic papers related to the use of tigecycline in cIAIs.

Methods

For this literature review we focused on papers dealing with health economics and resource utilization of the drug. We used several databases including PubMed and 42 unique Health Technology Assessment (HTA) organizations to find articles and then filtered the results to attain a more pertinent list to review. Figure 1. displays a summary of the search methodology and the subsequent selection process. The available literature will be discussed study by

study, but no comparison across the board or further meta-analysis will be attempted.

For search terms we used “tigecycline” in combination with “Health Economics,” “Resource Utilization,” “Cost-Effectiveness,” or “Length of Stay.” We excluded articles without abstracts, published over 10 years ago, or not in English. Articles were then selected for eligibility using four additional inclusion criteria: 1) we excluded all articles not explicitly discussing cIAs (Indication); 2) we excluded articles analysing tigecycline’s efficacy for one particular pathogen and/or with pathogens not commonly found in cIAs (Bacteria Type); 3) we excluded studies that were topically relevant to the search but did not yield usable information (Qualitative Assessment); 4) we excluded studies that were relevant but had incomplete methodology or did not undergo a peer-review process (Technicality).

Results

Combining the multiple search requests using the keywords as described in the Methods, results in a total of 49 items, of which 9 show up in more than one query. After eliminating five duplicates and four triplicates there remain 36 unique papers, four of which either do not have an English abstract or were over 10 years old. A total of 32 full text publications were then retrieved in which one was excluded due to not being in English and 22 were excluded due to a different indication other than cIAs being studied. We identified nine relevant articles (table 1) on the resource utilization of using tigecycline to treat cIAs. Nearly all of the rejected material (21 articles) was

eliminated because it failed the indication criterion, most of them covered pneumonia or complicated skin and soft tissue infections instead of cIAs. Of the final nine papers, three of these presented clinical studies and the remaining six were review articles.

Eandi, 2009.

Eandi examined the economic factors surrounding the management of cIAs within the Italian National Health System, the Italian system being no different from any of the other regions studied. It was reiterated that the initial antibiotic therapy choice is crucial to the quantity of healthcare resources used. Using tigecycline, which has the highest acquisition cost of the drugs included in this study, the overall costs, based on a decision model implemented on international outcome data and Italian costs, were comparable to that of other treatments. In fact, the mean cost of antibiotic acquisition made up only a small fraction of total hospitalization cost (less than 9%). Greater efficiency is achievable mainly through the reduction in rates of non-appropriate first-line antibiotic choices. [10]

Di Carlo *et al.*, 2013.

Di Carlo *et al* conducted a clinical study of treatment outcomes administering tigecycline (combined with colistin) on a select group of patients. The sample comprised all patients having undergone abdominal surgery encountered at the ICU of a particular centre (“Paolo Giaccone” University Hospital in Palermo, Italy) within a particular time frame (one year) with a particular mono-microbial bloodstream infection (KPC-Kp strains). The paper provided a few details

of the medical history for each patient in the small group (n=30), listing the various surgical indications and surgical infections. All of the microbe strains were resistant to a large number of conventional antibiotics. The authors examined the overall mortality rate and pursue a univariate analysis of risk factors. The results of the study showed that patients treated with high doses of tigecycline had lower mortality (P = 0.005) and a significantly favorable outcome per the Kaplan-Meier curve. However, the authors mentioned a FDA and EMA warning indicating a higher mortality rate in patients treated with tigecycline. [11]

Mallick *et al.*, 2007.

Mallick and colleagues conducted an analysis of pooled data from two multinational, double-blind clinical studies explicitly comparing two new generation antibiotics, tigecycline vs. imipenem-cilastatin, in hospitalized adults with cIAIs. The patients were randomized to receive either drug regime and the study looked at a number of outcome parameters, such as efficacy, clinical cure rate, safety, side effects, and health care resource utilization. Using multiple regression models and employing a data mining approach, the study sought correlations between health care utilization variables against baseline and on-treatment covariates. The clinical cure rates for the treatment of cIAIs were nearly identical for tigecycline and imipenem-cilastatin and none of the health resource utilization measures showed significant differences. However, the analysis revealed external factors, such as age or the presence of an intra-abdominal abscess, which predict increased treatment costs. [12]

Fomin *et al.*, 2008.

Fomin and colleagues conducted an analysis of data from the European sites that participated in two Phase 3, double-blind trials that compared tigecycline and imipenem/cilastatin in patients with cIAIs (c.f. Mallick *et al.*). For the purpose of the analysis the authors examined two populations: those that were coprimary microbiologically evaluable and those in the microbiologically modified intent-to-treat population. Clinical cure rates were measure at the test-of-cure visit. In either group tigecycline showed marginally better results which were, however, not significant. [13]

Wilke, 2010.

Wilke conducted a review of the literature concerned with the economics of current therapies used to fight multi-resistant bacteria. First the paper identified the major cost drivers of a therapy which include: prolonged length of stay, hours of mechanical ventilation, duration of treatment on an intensive care unit, cost of isolation and complications. The review focused on studies which examined the cost effectiveness and economic impact with respect to four modern antibiotics: linezolid, daptomycin, doripenem, and tigecycline. These agents, introduced to treat multi-resistant bacteria encountered in skin and soft tissue infections and hospital acquired pneumonia, are compared in relation to older therapy regimens. Tigecycline was commended based on its very broad spectrum of activity and, quoting the Reygeart review, the author argued that the drug could potentially lower cost when used as a monotherapy. In addition, Wilke pointed to the lack of “real life” data in evaluating economic impact, rather than relying on

pharmaco-economic models. In summary, Wilke concluded that "using modern antibiotics in whole is not more expensive than using established therapies. Modern antibiotics are cost-effective and sometimes even cost-saving." [14]

Nicolau, 2009.

Nicolau reviewed the literature on the clinical utility specifically for tigecycline, in the context of multidrug-resistant pathogens. The author examined published studies on efficacy, clinical use, safety and adverse effects, effectiveness in vitro and history against multi-drug resistant strains. In a brief section on cost effectiveness Nicolau compared the wholesale price of tigecycline (presumably in the United States) with that of imipenem/cilastin, aztreonam (both comparable) and vancomycin (1/3 to 1/4 compared to the other, but the cost must be weighed against additional labor associated with potential drug resistance). The paper ended with an Expert Opinion stating "tigecycline has been reviewed in the context of a position of strength in its role against emerging resistance in a broad range of organisms". [15]

Blot *et al.*, 2012.

Blot *et al.* presented a general treatise on therapies to treat intra-abdominal infections, listing recommendations by the authors supplemented by published reports. First the paper stressed the need for surgical source control and then examined factors to take into account when selecting antimicrobial therapies. After explaining the conventional divisions of intra-abdominal infection an alternative classification scheme is proposed, re-defining what constitutes

cIAIs. Based on this classification grid the authors made recommendations for selecting the most appropriate antimicrobial regimen. However other factors needed to be assessed, such as microbiological considerations, Penicillin allergies, and local epidemiology of drug resistance. Tigecycline was listed as one of the recently introduced treatment options (in conjunction with doripenem and moxifloxacin). The authors prescribed that tigecycline be positioned as a single agent first-line therapy due to its spectrum (but not in cases involving *Pseudomonas*). They also suggested that tigecycline be used in areas with a high prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) due to its activity against MRSA. [16]

Reygaert, 2010.

Reygaert provided a tutorial on intra-abdominal infections and skin and skin structure infections, developing the case for how the introduction of the new antibiotic tigecycline will have beneficial consequences. First a classification scheme for each of the diseases was established, defining the conditions when they are considered complicated infections. Subsequently, the author listed the numerous bacteria responsible for these pathologies, observing that complicated infections are most likely polymicrobial in origin. The review proceeded to enumerate the large number and wide variety of microbes which are resistant to many conventional antibiotics. Therefore the correct choice of antibiotic is critically important from the onset, given the effect on treatment outcome and the resulting economic impact, and further considering complications caused by secondary factors, such as comorbidities or incidence of diabetes. Under these

circumstances tigecycline recommends itself as a valuable addition to the available treatment options for difficult to treat patients due to its broad spectrum of activity against different types of bacteria. Used either as a monotherapy or in drug combination tigecycline promises an excellent chance of success, leading to lower cost and decreased mortality. [17]

Dunn, 2006.

Dunn conducted a review of the literature specifically for tigecycline focusing on the effectiveness against cSSIs and cIAIs. This study was undertaken in view of the need for new agents to combat microbes' resistances to available antibiotics. The paper listed current therapy options, including a number of newly developed drugs which have already reported resistances or are ineffective against specific strains. The mode of operation and the clinical effectiveness of tigecycline are treated in detail (c.f. Doan review[8]) to explain how it meets the need for new drugs. Citing two papers using the same data from two randomized, double-blind, international studies, the author reported either no or a slight improvement in resource utilization for tigecycline over another established antibiotic, vancomycin (depending on paper consulted). However, the review concludes that potential cost benefits could result from tigecycline's good patient acceptability and broad spectrum of activity, reducing adverse events and treatment failures. [18]

Discussion

While a search on Pubmed for publications on tigecycline returns 1683 entries going all the way back to 1999,

most of the papers do not concern the subject of this review, namely the health economic aspects in case of tigecycline treatments against cIAIs. Actually many of these studies examine *in-vitro* reactions and the microbiology of the drug against a variety of microbes. In fact, an extensive review article on tigecycline [9] features 101 references, but none of them cover health economic matters.

In search of the relevant literature we refined the criteria used to explore the medical databases, applying composite keywords, with the drug name in combination with terms signifying economic parameters. We considered several approaches before finally settling on the procedure described in the Methods section. In addition we tried expanding the unfiltered base material using "hospitalization" as keyword, but this scheme was abandoned because the new articles didn't provide any useful material. In order to maximize the return of relevant material we first looked for any study about the resource utilization during tigecycline therapies and removed papers not dealing with cIAIs subsequently. Indeed, a substantial number of articles concerned pneumonia for which the drug is indicated but which is not for discussed here.

Altogether thirteen Phase 3 and / or Phase 4 double-blind clinical trials have been conducted involving tigecycline; amongst these, five of them investigated patients with cIAIs in multi-centre studies comparing the effectiveness of tigecycline against another agent. A range of antibiotics served as comparators, from imipenem/ cilastatin (Tigecycline 301 and 306 Study Group) to vancomycin/ aztreonam (Tigecycline 300 and 305

Study Group) to ceftriaxone (Tigecycline 400 Study Group). Three other study groups examined the action of the drug against cSSSI. The final selection of 9 papers, three research articles and six reviews, relies predominantly on data provided by these studies: one research article presents results from the Tigecycline 300 and 305 Study Group, the other two report on data from confined studies at two centers in Italy; several of the reviews also refer extensively to the various Study Groups.

One of the goals of this review was to examine the global health economic outcomes for the use of tigecycline in cIAIs. Indeed our unfiltered search yielded studies from a wide range of locations, including Greece, Thailand, Taiwan, and Detroit. But the articles relevant specifically to the topic of this review are more restricted, being confined to the centers participating in the tigecycline Study Groups and a number of institutions in Italy.

Despite the limited dataset and the small number of relevant papers available a number of common themes emerge from the collection included in this review:

Several articles take note of tigecycline's broad spectrum of activity [16, 17]. In particular, the drug has been shown to be effective against MRSA infections [15]. While broad spectrum effectiveness is predominantly based on in vitro pharmacokinetics there is some direct evidence to substantiate this argument, based on reports of successful treatments against micro-biologically identified agents which are referenced.

There is general agreement that tigecycline therapy is safe and mostly

well tolerated, adverse events being mild to moderate in intensity. It does not damage the kidneys and appears to exhibit no ototoxicity. While in the Phase 3/ 4 studies a rather high percentage of subjects reports adverse events (11) (about 3/4 of them, equally in the tigecycline cohort and the comparator group), in only a small minority were the effects sufficiently severe to warrant discontinuation in the study (less than 2% of patients, due to most common discomfort, [19]).

Thirdly, several studies in multi-centre clinical trials have found that tigecycline performed well against each respective comparator, both in terms of medical efficacy and in terms of resource utilization. Despite the high acquisition price of the drug compared to many alternatives its use may still turn out to be competitive taking into account overall cost including reduction in resources use. In the context of increasing numbers of bacteria exhibiting resistance to commonly used antibiotics having another competitive agent available provides additional options in the treatment of cIAIs.

One limitation of this study appears to be that it excluded non-English articles. However, we are certain not to have accidentally limited our global reach to the Western Hemisphere as our search provided very little material in a foreign language. In addition, we did not conduct a meta-analysis to combine the results from individual study results which cannot therefore be directly compared.

Perhaps the major limitation of this review is the paucity of studies examining and analysing the economics

of tigecycline treatment regimes. Some rough calculations will be presented below. As in all the papers dealing with this subject health resource estimates invariably are based on economic modelling, instead of collecting and processing the actual data from the clinical studies. Such market-based research may be particularly important since the relative price of the drug varies substantially across different regions. For instance, domestically the cost of tigecycline is comparable to that of other modern antibiotics, whereas abroad there may be a significant price differential. On the other hand, the expenses for drug acquisition may play a minor part in the actual total cost of hospitalization. Thus gathering real data during clinical studies will provide critical information about the health care resource utilization in the course of tigecycline therapies.

This is a health economics and outcomes research (HEOR) study, and this systematic review helps decision-makers allocate treatment choices among competing therapies. The average cost of stay in the United States for cIAIs/cSSSI is between \$1600 and \$2100 per day and in a recent study by the US Centers for Disease Control, they estimated 870,000 cases of annual hospital admissions in the United States with a rising trend which results in a significant economic burden. Given the potential number of cases and the high costs associated with cIAIs/cSSSI, payers may require HEOR studies to help with the decision-making process given current budget constraints.

Due to the emergence of antimicrobial resistant bacteria, no single treatment is the answer to every cIAI over the comparators. Different local resistance patterns must come into play during the

selection process as these patterns have a large influence on the overall treatment cost and resource utilization rates. HTA organizations could be tasked with making recommendations on the choice and use of antibiotics for cIAIs/cSSSI. These organizations exist on national levels (e.g. National Institute for Health and Clinical Excellence in the United Kingdom) and on the local level (e.g. Technology Evaluation Center within Blue Cross and Blue Shield Association in the United States). This analysis may serve as a key piece of evidence for these HTAs during their assessment process.

FIGURES

Figure 1: Search Diagram

TABLES

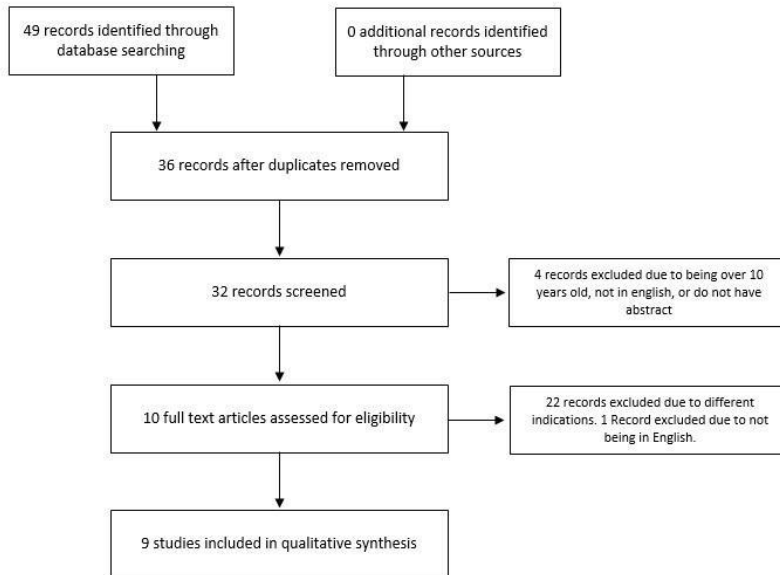


Table 1: Study Descriptions

Title	Author	Journal	Year	Description
Hospital management of complicated intra-abdominal infections: pharmaco-economic evaluation	Eandi	Journal of Chemotherapy	2009	An examination of how cIAls are treated in the Italian National Health System.
Klebsiella pneumoniae ST258 clone infection in postoperative abdominal surgery patients in an intensive care setting: analysis of a case series of 30 patients	Di Carlo, et al.	BMC Anesthesiology	2013	The study assessed the mortality of patients with KPC-Kp strains treated with tigecycline.
Predictors of efficacy and health resource utilization in treatment of complicated intra-abdominal infections: evidence for pooled clinical studies comparing tigecycline with imipenem-cilastatin	Mallick, et al.	Surgical Infections	2007	A pooled analysis of two clinical trials which assessed the efficacy, safety, clinical cure rate, side effects, and health care resource utilization of tigecycline and imipenem-cilastatin..
The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections - the European experience	Fomin, et al.	Journal of Chemotherapy	2008	An analysis of all the European sites from two phase III clinical trials of tigecycline.
Multiresistant bacteria and current therapy - the economical side of the story	Wilke	European Journal of Medical research	2010	A literature review focused on the economics of treatment in multi-resistant bacteria.
Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline	Nicolau	Expert Opinion Pharmacotherapy	2009	A literature review around tigecycline and its clinical utility in the context of multi-resistant bacteria.
Essentials for selecting antimicrobial therapy for intra-abdominal infections	Blot, et al.	Drugs	2012	A review of the current state of cIAI in addition to the available treatments.
Antibiotic optimization in the difficult-to-treat patient with complicated intra-abdominal or complicated skin and skin structure infections: focus on tigecycline	Reygaert	Therapeutics and Clinical Risk Management	2010	The paper reviews cIAls and cSSTIs and how new treatments such as tigecycline will have beneficial consequences.
Tigecycline: an evidence-based review of its antibacterial activity and effectiveness in complicated skin and soft tissue and intraabdominal infections	Dunn	Core Evidence	2006	A review of the literature focusing on the impact of tigecycline in cIAls and cSSTIs.