Review Article

Burden of Antibiotic Resistant Gram Negative Bacterial Infections: Evidence and Limits

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Abstract

Infections due to antibiotic-resistant Gram-negative bacteria unquestionably have substantial effects on morbidity and mortality. However, quantifying the exact economic burden attributable to these infections still remains a challenging issue. The review of the literature on this subject shows that severe infections from Gram-negative bacteria are associated with increased economic burden. However, the low comparability of methods and results limit the possibility to draw a clear conclusion. A better collaboration between health economy and clinical research is advocated to produce specific guidelines for economic studies in medical research.

Keywords: Multidrug resistance; Burden; Cost

Introduction

Over the last years several European reports have established that severe infections due to Gram-negative bacteria, including those by strains resistant to multiple classes of antibiotics (MDR), are significantly increasing. Some of these reports observed the cases by gram negative bacteria surpassing the episodes due to gram-positives such as Methicillin-Resistant Staphylococcus Aureus (MRSA) and Vancomycin-Resistant Enterococci (VRE) [1,2]. According to the most recent epidemiological report of the European Antimicrobial Resistance Network (EARS -Net) of the European Centers for Disease Control and Prevention (ECDC), bacteraemias due to MRSA and VRE in Europe are stable and even decreasing in some countries, while cases due to Gram-negative bacteria, especially third-generation cephalosporins-resistant Enterobacteriaceae, MDR Acinetobacter baumannii and Pseudomonas aeruginosa are increasing [1]. In 2009, ECDC and the European Medicines Agency (EMEA) published the results of an epidemiological study on the frequency, costs and impact of sepsis caused by the most important antibiotic-resistant bacteria, drawing the following conclusions: first, the antibiotic resistance is high among both gram- positive and gram-negative bacteria, reaching 25% in many European countries; second, the resistance rate is increasing, especially among gram-negative bacteria; and third, each year about 25,000 patients die from infection sustained by an antibiotic-resistant bacteria in Europe and about two-thirds of these deaths are due to infections by gram negatives [3]. The same study revealed that, in 2007, the economic burden of MDR bacterial infections in Europe was approximately 1.5 billion euro. The costs associated with infections by MDR gram-negative bacteria were significantly higher than the costs associated with infections due to gram positives. These costs were primarily direct in-hospital costs and costs for lost productivity due to the death of the patients. Importantly, data from outpatients were not collected. This limitation of the study suggests that these numbers represent an underestimation of the true extent of the problem.

The Evidence

Ten studies [4-13] published between 2006 and 2013 evaluated the economic impact of infections caused by MDR gram-negative bacteria according to different study designs, protocols and analysis (Table 1). Half of these studies was conducted in the USA [4-7,9], 3 studies were conducted in Asia [8,10,11] and only 2 studies in Europe [12,13]. All studies used retrospective design, eight were cohort studies [4-6,9-13] and two paired matched case control studies [7,8]. Different species of Gram-negative bacteria have been included. Three studies [4,9,10] evaluated the impact of infections caused by Gram-negative bacteria overall, with no distinction of species. Four studies included infections due to Enterobacteriaceae [7,11-13], one including any species of Enterobacteriaceae [12], three including Escherichia coli [7,11,13], two Klebsiella spp. [7,11] and one Proteus spp. [11]. Two studies evaluated the impact of infections due to non fermentans gram-negative bacteria [5,6]. The definition of "resistance" was extremely heterogeneous across studies. Resistance to at least one antibiotic class was considered in two studies [4,9], and to at least three classes in other two studies [8,10]. The production of extended-spectrum beta-lactamase (ESBLs) in Enterobacteriaceae was evaluated in 4 studies [7,11-13]. Lautenbach et al. [5,6] assessed the impact of infections due to P. aeruginosa and A. baumannii resistant to carbapenems. Five studies included bacteraemias only [8,10-13], and the remaining any kind of infections, with the exclusion of urinary tract infections in the study by Lee et al. [7].

All but one [5] studies documented a significant increase in the cost and length of hospitalization of infected patients with antibiotic-resistant gram-negative bacteria compared to patients infected with susceptible bacteria. According to these data, there seems to be solid evidence that antibiotic resistance in gram-negative bacteria invariably impacts on hospital costs (Table 1).

The Limits of the Evidence

The strength of the scientific evidence needs, however, a critical overview of the limitations. The most important limit relies on the lack

of comparability of methods, and consequently, of the results of the studies. The estimates provided by the reviewed studies are markedly different (see Table 1). These differences derive, on one side, from the characteristics of the study protocol , such as the type of infection and the bacterial species considered, the combination of antibiotic resistance, and, not least, the currency used. There are, on the other hand, a number of factors linked to the methodology of the study which might influence the results of an economic study [14]. All these differences generate a lack of compactness and comparability of the methods used to derive the estimate of the economic impact and, consequently, considerable difficulties in determining the actual size of the problem.

Author, year	Country	Type of study	Cases	Controls	Type of infections	Main results	Limits
Evans, 2007 [4]	USA	Retrospective study	Gram negative bacteria, resistant to at least one antibiotic class between aminglicosides, cephalosporins, carbapenems and quinolones	Susceptible gram negative bacteria	All kind of infection	Increase of the length of hospitalisation among cases compared to controls (29 versus 13 days); increase of total hospital cost among cases compared to controls ($80,500 versus $29,604)	Single centre; analysis not stratified according to the type of infection and bacterial species.
Lautenbach, 2009 [5]	USA	Retrospective study	Imipenem resistant A. baumannii	Imipenem susceptible A.baumannii	All kind of infection	No difference of length of hospitalisation and costs between cases and controls	Selection bias
Lautenbach, 2010 [6]	USA	Retrospective study	Imipenem resistant P. aeruginosa	Imipenem susceptible P.aeruginosa	All kind of infection	Increase of the length of hospitalisation among cases compared to controls (16 versus 9 days); increase of total hospital cost among cases compared to controls ($251,495 versus $166,196)	Selection bias
Lee, 2006 [7]	USA	Retrospective study	ESBL positive E. coli e Klebsiella spp.	ESBL negative E.coli e Klebsiella spp.	All kind of infection with the exclusion of urinary tract infections	Increase of the length of hospitalisation among cases compared to controls (mean difference 9.7 days, 95% CI 3.2-14.6); increase of mean total hospital cost per patient among cases compared to controls (16,450$, 95% IC $965-31,937)	Small sample size; Analysis not adjusted for severity of illness and time at risk; analysis not stratified according to the type of infection and bacterial species
Lee, 2007 [8]	Taiwan	Retrospective study	MDR A. baumannii (resistant to penicillins, cephalosporins, anti-pseudomonas quinolones, aminoglicosides and cotrimoxazole, and sensitive to carbapenems)	No MDR A. baumannii	Bacteraemia	Increase of the length of hospitalisation among cases compared to controls (13.4 days); increase of mean total hospital cost among cases compared to controls ($3,758)	Single centre
Mauldin, 2010 [9]	USA	Retrospective study	Gram negative bacteria (Acinetobacter spp, Enterobacter spp, E.	Susceptible gram negative bacteria (Acinetobacter spp,	All kind of infection	Increase of the length of hospitalisation	Analysis not adjusted for severity of

			coli, Klebsiella spp, Pseudomonas spp) resistant to at least one class of antibiotics between quinolones, piperacillin, carbapenems or cephalosporins	Enterobacter spp, E. coli, Klebsiella spp, Pseudomonas spp)		among cases compared to controls (23.8%); increase of total hospital cost among cases compared to controls (29.3%)	illness and time at risk; analysis not stratified according to the type of infection and bacterial species
Ng, 2012 [10]	Singapore	Retrospective study	MDR Gram negative bacteria (resistant to at least 3 classes of antibiotics)	No MDR gram negative bacteria	Bacteraemia	increase of total hospital cost among cases compared to controls (45.7%, corresponding to 8,638 Singaporean $ per patient)	Analysis not stratified according to the type of infection and bacterial species
Schwaber, 2006 [11]	Israel	Retrospective study	ESBL positive E. coli, Klebsiella spp e Proteus spp.	ESBL negative E. coli, Klebsiella spp e Proteus spp	Bacteraemia	Increase of the length of hospitalisation among cases compared to controls (1.56 fold); increase of total hospital cost among cases compared to controls (1.57 fold corresponding to 13,417 shekels per patient)	Single centre
Stewardson, 2013 [12]	Switzerland	Retrospective study and multi state model	ESBL positive Enterobacteriaceae	ESBL negative Enterobacteriaceae	Bacteraemia	Increase of the length of hospitalisation among cases compared to controls (6.8 days); increase of total hospital cost among cases compared to controls (9,473 CHF per patient)	Single centre
Tumbarello, 2010 [13]	Italy	Retrospective study	ESBL positive E. coli	ESBL negative E. coli	Bacteraemia	Increase of the length of hospitalisation among cases compared to controls (7 days); increase of total hospital cost per patient among cases compared to controls (EUR 5,026)	Single centre

Table 1: Studies on the economic burden of infection by antibiotic-resistant gram-negative bacteria

Definition of the Study Perspective

The definition of the perspective of an economic study is of crucial importance [15]. The point of view of the hospital or, more generally, of the health system will produce completely different results from that of patients and the wider society. In the first case, the direct costs only, i.e. costs related to the health and the care of the patients, are taken into account. In the second case, indirect costs are also included, i.e. those costs related to lost productivity of patients and of those who take care of them. The perspective of the hospital is predominant among the studies that assess the economic impact of infections by MDR Gram-negative bacteria [4-13]. That means that the costs are solely related to the length of hospitalization, to the antibiotic therapy which is often more expensive, and to the visits, while the loss of productivity due to both the lack of work and, in some cases, premature death associated to these infections is completely excluded. The perspective of the hospital, often intrinsically linked to the hospitalization during which the infection under study has been diagnosed, does not take into account those infections which are less severe and then treated on outpatient basis. Finally, there are costs

related to infection by antibiotic-resistant bacteria, not specifically gram negative, which are different between points of care and can be more difficult to quantify, such as the costs related to infection control surveillance and screening of patients at risk of infection, and those arising from the use of prolonged antibiotic therapy and therefore at greater risk of antibiotic's side effects.

Costs definition (microcosting versus gross costing)

The definition of costs is an additional parameter that has a significant impact on the results. The choice between microcosting, i.e. the use of segregated data for individual unit cost, and gross costing or top-down costing, i.e. the allocation of a budget to specific services, such as hospitalization or visits, according to local regulations, depends on the local availability of such data in most cases [15]. Many studies use a combination of the two: at first, identifying and monetizing those cost determinants which have the greater economic impact, such as the length of hospitalization; and second, using the microcosting for the definition of additional direct costs. Among the studies reviewed, no one used the microcosting specifically for the assessment of the economic impact of MDR gram negative infections.

Study Methodology

As mentioned above, the methodology used by the majority of studies to evaluate the economic impact of infections caused by antibiotic-resistant bacteria is to assign fixed cost to cost determinants, especially to the length of hospitalization associated to the infection. The pattern is the following: first of all, identify the number of extra days that the patients with infection spend into the hospital compared to the patients without infection, that is a result of the infection itself and the health services used for additional the management and treatment of infection. Second, these additional days, and specific interventions are monetized for the calculation of specific costs attributable to the infection.

This methodology suffers from at least three sources of error: first, the estimated price may not reflect the real value of the resources; second, the fixed and variable costs are not always properly identified; and third, the estimate of the length of hospitalization attributable to the infection is prone to bias.

This last point has been extensively discussed among the scientific community. First, several patient-level factors, other than the presence of the infection, may be associated with a prolongation of hospitalization and to a greater use of health care resources. The omission of these confounding variables, such as co-morbidity of the patient or the severity of the clinical condition, can lead to misleading results. When assessing the impact of infection on the costs and length of hospitalization, the first challenge is to extract the independent effect of the infection on the outcome, taking contemporarily into account all the observable confounding factors. Comparative cohort studies, which combine infected cases and uninfected controls [16 -20] and that use multivariate regression analysis to enable control of a greater number of confounding factors [21-23] are commonly preferred to reduce the risk from this type of bias. Although the use of these statistical techniques represents a significant step forward, there remains the possibility of omission of important variables. As a result, the number of explanatory independent variables should be extended significantly to reduce the risk of confounding and increase the accuracy of the estimate. In an extreme example, Graves et al. [21] included up to 123 possible confounding variables in an analysis of the effects of nosocomial infections on the length of hospitalization, minimizing distortions arising from omitted variables. Although it has been observed that the successful completion of an observational study can achieve results comparable to those of randomized controlled trials [24], reproducing the model proposed by Graves et al. would require a disproportionate investment of resources for the type of study, which , having been observational , remains subject to other sources of bias. In addition, a so extensive data collection is not feasible in retrospective studies [4-13].

Another strategy used to reduce confounding in estimating the excess of hospitalization associated with infection is matching infected cases to uninfected controls, according to confounding variables, such as demographics, indicators of severity of disease, and other factors related to the length of hospitalization. However, the matching factors used in the various studies are different, suggesting that identification cannot be simple. A study published in 2010 showed that the greater was the number of confounding variables included in the pairing process, the lower was the increase in the length of hospitalization and the costs associated with sepsis in 1839 patients from 19 hospitals in Belgium [20]. The most important factor that influenced the final estimate was the time that the patient spent in the hospital before infection, which inclusion in the analysis led to a reduction in the prolongation of hospitalization from 21 to 7 days. However, the matching process can suffer from important sources of bias, like the selection bias [25]. In the study by Vrijens et al [20], the most accurate estimate was obtained in a sample corresponding to 50% of patients initially included in the analysis.

Another important source of bias occurs when infected and uninfected patients are compared with regard to the total cost or the entire length of hospitalization. Indeed, the days and expenses incurred after the occurrence of the infection are probably associated with the infection in infected patients. Modifying the analysis (i.e. the length of hospitalization post- infection of the cases is compared with the total hospitalization of controls) does not completely remove the distortion. The bias persists even in studies in which uninfected matched controls are selected as having a length of hospitalization at least as long as the duration of hospitalization before infection among infected cases [26,27]. So, these study designs have several limitations due to the time-varying nature of the exposure. They do not take into account the time-dependent nature of the associated infection, but treat them as events already determined. These studies, time-independent (or time fixed) suffer from a kind of bias called time-dependent bias, which leads to an overestimation of the effect [28 -34] . The multi-state model is an appropriate method to avoid time-dependent bias and provides a more accurate estimate of the length of hospitalization, as well as other in-hospital adverse events with an impact on the health resources [28]. The multi-state model describes several possible events and the transition between these events in a cohort of individuals. The state of the exposure (such as the occurrence of an infection) is considered time-dependent, therefore, individuals move from one state to the next (for example, "hospitalization", to "infection", and finally to "discharge") only when these events occur. The study proposed by Stewardson et al. [12] applied a multistate model to estimate the prolongation of hospital stay associated with sepsis by ESBL-producing Enterobacteriaceae, obtaining an estimate of 6.8 days and an increase in hospitalization costs of 9.473 CHF per episode.

Conclusions

Infections by MDR Gram-negative bacteria have indisputably a major impact on morbidity and mortality. However, quantifying the exact economic impact attributable to such infections remains a methodological challenge, since multifaceted and difficult to capture entirely. The reviewed studies show that, arguably, the MDR Gram-negative bacterial infections cause a significant economic burden. On the other hand, the lack of comparability of methods and results does not allow drawing the final conclusion. The communication between clinical researchers and economists should be improved for the development of transparent and reproducible guidelines. The improvement of the evidence is the basis for the evaluation of intervention strategies with the purpose of limiting the spread of MDR infections.

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