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Excess length of hospital stay due to healthcare acquired infections: methodologies evaluation

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Abstract

Background. *Healthcare acquired infections (HAI) cause an increase of burden and in particular excess length of hospital stay (LOS) accounts for approximately up to 90% of total costs. Therefore accurate estimation of extra hospital stay due to healthcare acquired infections is very important.*
Methods. *The authors carried out a review comparing the principal methods internationally used for estimating the excess LOS attributable to healthcare acquired infections.*
Results. *The methods described and analysed are: 1) Implicit physician assessment; 2) appropriateness evaluation protocol; 3) unmatched case-control; 4) matched case-control; 5) regression analysis; 6) multistate model. The various methodologies are described underlining advantages and limits which researchers need to know before starting any economic analysis.*
Conclusions. *Overall, studies taking into account the time-dependent nature of HAI show to give more precise and reliable results.*

Introduction

Healthcare acquired infections (HAI) are a recognized important cause of morbidity, mortality and economic burden for hospitals (1-4).

The increasing antimicrobial resistance raises concerns regarding the impact on patients with multidrug resistant organisms. Consequently important efforts have been made to study the clinical outcomes among patients infected with such pathogens, showing higher mortality and frequent treatment failure among them compared with those infected with the susceptible isolates (4-7).

While many findings have been achieved on clinical issues, our knowledge on the economic impact by multidrug resistant infections needs to be widened.

Overall, HAI economic burden is divided into direct and indirect costs. Direct costs are represented principally by additional hospital stay, drug treatment, medical and surgical procedures; indirect costs by the patients' salary loss, relatives' time and infirmity. Because it is difficult to evaluate exactly all variables, especially indirect

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costs, investigators generally estimate only direct extra costs and particularly length of hospital stay (LOS), which may account for approximately up to 90% of total costs (2, 3, 8-10).

Consequently, as researchers have developed various methodologies to assess the HAI-attributable extra stay, we decided to carry out this study to describe and evaluate them.

Implicit physician assessment

It is a subjective method, for each patient with a confirmed HAI diagnosis, the physician or trained nurse reviews the clinical record and any other relevant clinical information such as nursing record, laboratory data, X-rays. Considering all data and applying implicit criteria the reviewer judges whether any single day of hospitalization should be attributed to the HAI or not.

This system is simple and needs a limited amount of resources to be applied. Also, differently from the comparison methods, includes in the study only the cases and no controls.

Therefore, already in the 1930', it was adopted by some to evaluate the benefit of a new type of wound dressing (11). After the war, Goodall et al. (12) carried out a study in 13 wards of 8 hospitals and estimated an hospital prolonged stay of 21 days. Also others applied the same methodology to estimate the extra days of hospitalization caused by surgical wound infection (13) These various studies showed large differences in the final extended LOS reported estimates, may be because of differences in patient groups and data collection (14).

The implicit physician assessment primary disadvantages are represented by the high degree of subjectivity in applying implicit criteria and low interrater reliability for estimates of additional days of care.

This method consistently yields the lowest estimates of additional days due to HAI compared to other methods and is thought to underestimate the true incremental stay (15).

Comparing the implicit physician assessment to the matched comparison method Haley et al. (14) found that the former estimated extra days were 2.5 times less than the latter. The explanation may be that the reviewer tends to attribute extra days only if they are clearly the consequence of a nosocomial infection and therefore estimates obtained by this method might underestimate the true magnitude. However, this system may provide a valid minimal estimate (14).

Appropriateness evaluation protocol

The appropriateness evaluation protocol (AEP) was designed to overcome many of the methodological concerns associated with the historical cohort approach (16). This method assumes that all pertinent clinical information, in order to determine whether each day of stay can be justified by care for the original causes of the hospitalization or directly by the HAI, are contained in the medical record. The AEP is a diagnosis independent, objective method using explicit criteria to determine need for hospital admission and for each day of inpatient care.

In order to identify the additional days due to HAI, each day of hospitalization is evaluated twice using two different sets of criteria. The first (full AEP questionnaire) uses all the medical and nursing available information in the record, to determine whether each day in hospital is required for care of the patient including HAI. The second questionnaire (partial AEP), which excludes all information related to the treatment of nosocomial infection (e.g. antibiotics), identifies the days in hospital necessary in the absence of HAI. Therefore days of

Table 1 - Characteristics of methodologies to estimate excess lentgh of stay due to healthcare acquired infections

Methodology	Advantages	Limits	Quality
Implicit assessment	Easy to perform; Limited resources	Subjective method; Not standardized	Medium
Appropriatenss evaluation protocol	Eliminates controls bias; Objective method	Highly trained personnel; Questionnaires modification according to patients characteristics;	High
Unmatched case-control	Inexpensive; Readly available data	Controls bias; Overestimates incremental stay caused by infection	Low
Matched case-control (Not time-dependent matching)	Reduces partially the bias of unmatched conrol studies	Number of criteria may reduce available controls, excluding some cases from analysis	Medium
Matched case-control (Time-dependent matching)	Corrects the bias of unmatched conrol studies (Length of stay in controls not inferior to length of stay in cases fron admission to infection)	Number of criteria may reduce available controls, excluding some cases from analysis	High
Regression analysis	Includes almost all infected and uninfected patients	Highly trained personnel; Need to know specific clinical data	High
Multi-state model	Includes almost all infected and uninfected patients	Highly trained personnel; Need to know specific clinical data	High

hospitalization for which the full AEP review indicates need for acute care, but for which the partial AEP review does not, are attributed to the nosocomial infection. In short the only reason the patient is hospitalized is for management of the HAI (15).

Combining these two reviews yields one of the following decisions for each day reviewed: 1) HAI-attributed day where the full AEP review indicates yes and the partial AEP review indicates no; 2) non-HAI-attributed day where either the full AEP review indicates yes and the partial AEP review also indicates yes, or the full AEP review indicates no and the partial AEP review also indicates no (17).

The AEP system using the case as a control of itself eliminates some limits present in the comparison methods and it can be considered as an evolution of the implicit physician assessment (18-19). However, it needs highly trained personnel and the questionnaires (full and partial) require modifications according to the patients characteristics (20).

Unmatched case-control

The unmatched group comparison method determines the hospital extra stay by comparing two patient groups: those with and those without HAI. Differences in total hospital days between uninfected and infected groups are then attributed to the nosocomial infection. This system is based on the assumption that any difference in LOS between infected and uninfected patients is attributable to the HAI. Generally the comparison is carried out using the average stay of cases (infected) and of all the other patients (uninfected) (15).

The major advantage of this method is represented by the use of inexpensive,

readily available LOS data. The principal disadvantage is the implicit assumption that any difference in extra stay is attributable only to infection and not related to any other inherent difference between the two groups. The HAI group may have a propensity for longer LOS independently from any infection. Haley et al. showed that the estimates by the unmatched method were 25% greater than the matched estimates (14).

Therefore, this system is considered to overestimate the incremental stay caused by infection and may represent an upper limit for increased attributable days (8, 15). Also it could be useful to give rapid estimates of extra costs, but would need to be followed by more precise and analytical studies (21-22).

Matched case-control

This system overcomes the limits of the unmatched comparison method by matching patients who have an HAI with similar but uninfected controls using criteria such as age, sex, surgical procedure, diagnosis, risk factors, gravity score (APACHE, SAPS II). Extra hospital stay is estimated by subtracting the LOS of the controls from the LOS in cases. The difference is directly attributed to the infection (15).

For each infected patient is selected an uninfected hospitalized patient and matched with the patient according to a hierarchy of characteristics such as discharge diagnosis according to the International Classification of Disease Ninth Revision – Clinical Modification (ICD-9-CM) code, inpatient areas, the main procedure performed at the first surgical procedure, gender, and age. An ideal matching should include all potential confounding factors and to improve the matching a point scoring system has been introduced to quantify the appropriateness of control matching.

This method assumes that patients developing HAI are not otherwise predisposed to requiring longer LOS independently of the infection. Second, an ideal case-control matching process should incorporate the full range of potential confounding variables, and this data are not always available. Thus, as the number and specificity of variables used to match cases and controls increase, the potential pool of control matches may be insufficient and result in the exclusion of cases for which no control can be matched (17).

Of various methods used to estimate extra hospital stay caused by HAI the matched case-control method is among the most appropriate and used (2, 9). Many researchers adopted it even for large studies (23-27).

However, because it assumes that any difference in LOS is attributable to infection and not related to other inherent differences between the two patient groups, it is generally considered to overestimate slightly the attributable days and costs (15, 17, 28-29).

To improve matching some investigators introduced a point scoring system which measures precisely the matching appropriateness of controls (10).

Other authors included additional criteria: the LOS of the controls should not be less than the time interval between admission and infection of the cases. Matching methods should match on time to infection requiring that the control patient have to spend an equivalent time in hospital. This not completely eliminates time-dependent bias but it significantly reduces it. Once the pairs are matched, the estimation of the number extra days is obtained subtracting the LOS of the non-infected patient from that of the infected patient and then averaged the extra LOS (8, 10, 28-30).

Regression analysis

Matching presents some disadvantages, as matching for many variables requires a substantial increase in the size of the pool

of controls which is not always possible, and matching too few variables might cause bias from "omitted variables" because important factors that explain the variation in cost outcomes are excluded. The consequence is that the cost attributed to HAI may be either overstated or understated. Also, if case patients are subsequently excluded from the study to match more variables (ie, to mitigate bias from omitted variables), then a selection bias arises because not all case patients have the same opportunity to be included in the comparison of cost outcomes. Use of statistical regression analysis for a cohort of patients can avoid selection bias completely and presents an opportunity to reduce bias from omitted variables (31).

The regression analysis approach enables the inclusion of almost all infected and uninfected patients in analysis, and therefore provides a means to avoid selection bias. Though vulnerable to the influence of endogenous variables, methods such as instrumental variable models have been developed in order to minimise the effects (2, 9, 32-33).

Regression analyses had not been used for extra LOS and costs estimations in the 1980s. In the 1990s, there were three studies that had used regression analyses, and this number rose over 20 after 2000 (2, 32, 34-35).

Multistate model

The multistate model is a suitable method to avoid time-dependent bias, offering a more precise estimation of extra LOS attributable to HAI, as well as many other cost-consuming in-hospital adverse events (36). The structure of a multistate model can be viewed as unexposed individuals moving into the exposure state only when the exposure occurs and into the final state when the study endpoint is observed. In a multistate model assessing the excess of LOS associated with HAI, the occurrence of HAI would be the time-dependent exposure status, and discharge and deaths would be the study endpoint, also discharge and death can be handled as separate outcomes (36). Many studies are carried out by this method (37).

However, multistate models have also some limitations. First, because a multistate model is a representation of events as they occur over time, individual patient-level data need to be collected on a daily basis and this may be costly in terms of labour. Second multistate models rely on two restricting assumptions: the probability of transition into the next state depends only on the current state, that is the future course of a patient (such as to be discharged or to die) is assumed to depend on the current HAI status and not on the time its diagnosis; it assumes that the exact time of the appearance of a HAI is known. The first restriction may be resolved by including the time since HAI diagnosis in a regression model for the multiple states. The second restriction might be more relevant in clinical trials with periodic follow-up visits of patients than in a hospital setting, where daily data records are currently available. Finally, the statistical analysis requires advanced statistical expertise (36). Also, a limitation of multi-state models in the past was that they were not able to control for patient characteristics (9).

Discussion

Overall methodologies characteristics to estimate excess LOS due to healthcare acquired infection are reported in Table 1.

The AEP-based method has the following advantages: the possibility to enroll all patients with HAI, evaluation based on the pattern of the care provided, availability of information in the medical records resulting in a greater accuracy for studying HAI. Extra LOS estimated with the AEP method is

smaller than with the matched and unmatched comparison. The AEP method may distinguish between extra LOS associated with infection and extra LOS because of treatment of the principal clinical problem for which the patient was hospitalized; the method make known cost distribution of various type of infection in different ward providing useful information for setting priorities in infection prevention programs. The method uses the patient as their own control and it corrects the common flaws of methods based on the assumption that the resources used by HAI can only be determined by measuring extra days of LOS of infected versus non infected patients: for these reasons, it appears to be more reliable than the other two classical methods (8, 18).

The unmatched and matched comparison methods produce different results because they change populations for comparison. The unmatched comparison compares patients with and without HAI, but this assumes that the two populations are homogeneous and does not consider potential risk factors which create a net difference between the two. The validity of the matched comparison depends on the quality of matching and a straight match can reduce the effects of confounding where severity of illness was accounted for. The adjusted mean difference in LOS between infected and uninfected patients is reduced when matched for age, gender, ward, primary diagnosis, comorbidity and surgical operations which, significantly reduced the average difference on the total level.

Ideally, matching should obtain controls with the same risk factors of stay prolongation as cases, except for the presence of HAI. The main risk factors associated with increased LOS are age, discharge diagnosis or accompanying diseases, and complications during hospital stay. Because patients with HAI more frequently have other comorbidities associated, the matching may select controls systematically less ill than cases with a shorter duration of stay (selection bias). Furthermore, it is often difficult to find a control with the same characteristics of the patient and to include more background and risk factors would reduce the differences between the groups, but such an inclusion would on the other hand make the interpretation of the outcomes more difficult. This may lead to cases exclusion for which no control can be matched, resulting in the selection of a less representative subset (8, 19, 28).

Independently of the matching problem, because only the LOS between the two groups (with and without infection) and not the pattern of the actual care rendered to the patient was taken to assess the HAI-attributable days in the unmatched and the matched comparison methods, it remains uncertain whether the differences may be really linked to the HAI. Several HAI-attributable days of stay based exclusively on differences in LOS may reflect differences in the basic care process, physician preferences and practices, and internal operational inefficiency that effect LOS rather than the presence of a HAI (17). Matching controls by "length of stay in controls equal to interval from admission to infection in cases" is considered a fundamental criterion as it allows to match on the timing of the infection minimizing significantly a possible bias (2, 9, 10).

Although regression models can be very useful, when electronic data are available, to carry out studies on large populations, recent literature shows that the most interesting approach to estimate excess LOS is today represented by multi-state modelling (9).

Overall these methods can be grouped as "time-fixed" and "time-varying" according to their treatment of time dependence. Patients acquire HAI during their hospital stay, thus they have already spent some time in hospital before they become infected. This time requires specific consideration in the analysis by treating HAI as a time-dependent exposure. Many studies are prone to the "time-dependent bias", including studies

that fail to treat nosocomial infection as a time-dependent exposure (38-39), therefore estimates from time-varying methods that control for time-dependent bias should be adopted (40).

Beyersman et al. (41) show that time-dependent bias is large in methods such as regression analysis and survival analysis that do not normally treat HAI as a time-varying exposure. Widely used regression methods cannot control for the timing of events and caution should be exercised when applying or interpreting regression results. Regression methods to estimate excess LOS should only be used for associations rather than causal inference (38).

Matching methods should match on time to infection, requiring the control patient to have spent an equivalent time in hospital before the infection as the case (9). This might not completely eliminate independent bias but it will significantly reduce it. Nelson et al. compare three estimation strategies and show that matching on the time to infection can substantially reduce the bias (42).

The alarmingly increasing antimicrobial resistance raises global concerns regarding the impact on patients with MDR infections, which are expected to be more costly for healthcare systems than susceptible ones, as they cause a higher LOS in the hospital (43-49). According to previous studies, a relevant increase in hospital stay following HAI due to multi-resistant organisms was found (4). Also these multiresistant infections put greater difficulties in prevention (50-52).

In addition to time dependence bias, studies should consider carefully case definitions, causative organisms, populations characteristics, risk factors and antimicrobial resistance in order to provide accurate data to support effective and efficient infection prevention and control interventions (2, 4, 9). Differentiating between endemic and outbreak conditions (53). Among the latter there are some specific microorganisms on which there is limited data on costs (54-58).

Conclusions

Over the last decades various methodologies have been developed to assess excess LOS due to HAI, but quantifying the exact extra stay remains a challenging issue.

The AEP methodology is well designed eliminating some limits present in the comparison methods, but has not been widely adopted because needs highly trained personnel and the questionnaires (full and partial) require frequent modifications according to the patients characteristics.

Unmatched case control studies have been largely used in the past but, because they overestimate the incremental stay caused by infection, there use today is limited.

Overall, studies that take into account the time-dependent nature of HAI show to give more precise and reliable results. Therefore, it is essential that matched methods should match on time to infection, requiring the control patients to have spent an equivalent time in hospital before the infection as the case (Tab. 1).

Similarly, regression and multi-state studies need to include time-varying exposure.

In addition to time dependence bias, studies should consider carefully case definitions, causative organisms, populations characteristics, risk factors and antimicrobial resistance in order to provide accurate data to support effective and efficient infection prevention and control interventions.

Riassunto

Extra degenza ospedaliera causata dalle infezioni correlate all'assistenza: valutazione delle metodologie

Introduzione. Le infezioni correlate all'assistenza (ICA) causano un aumento dei costi ed in particolare l'extra degenza ospedaliera costituisce circa il 90% dei costi totali. Quindi una stima accurata dell'extra degenza ospedaliera causata dalle infezioni correlate all'assistenza è molto importante.

Metodi. È stata effettuata una rassegna dei principali metodi impiegati a livello internazionale per stimare l'extra degenza ospedaliera attribuibile alle infezioni correlate all'assistenza.

Risultati. I metodi descritti ed analizzati sono stati: 1) l'autovalutazione del medico; 2) il protocollo di valutazione dell'appropriatezza; 3) il caso-controllo senza matching; 4) il caso-controllo con matching; 5) l'analisi di regressione; 6) il modello multi-stato. Le varie metodologie sono state descritte sottolineando i vantaggi ed i limiti che i ricercatori devono conoscere prima di iniziare un'analisi economica.

Conclusioni. In generale, gli studi che includono la natura tempo-dipendente delle infezioni correlate all'assistenza si mostrano più precise ed affidabili nei risultati.

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