RETROSPECTIVE OR CLUE-BASED SURVEILLANCE? WHAT IS THE IMPACT ON THE NOTIFICATION OF SURGICAL SITE INFECTIONS IN CARDIAC SURGERIES

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ABSTRACT

Objective: to assess the impact of surgical site infections reported by clue-based surveillance compared to those detected by the retrospective assessment of the patient’s medical record.

Method: epidemiological study and reflection conducted in a large, public, university hospital.

Results: the data collection was carried out through register of notifications by clues, performed by the infection control commission and analysis of the medical records of patients submitted to cardiac surgeries between 2011 and 2014. The diagnosis of surgical site infection followed the criteria defined by the National Healthcare Surveillance Network of the Centers Disease Control. The data were analyzed in the Epi-info® 6.4 program, through descriptive statistics. A total of 294 patients undergoing cardiac surgeries were analyzed by clue-based surveillance and 195 by the review of medical records. 17 (65.9%) superficial surgical site infections were reported; one that was deep (3.8%); eight (30.8%) of organ/cavity in clue-based monitoring; 25 (69.4%) superficial incisors; two (5.6%) deep ones, and nine (25%) of organ/cavity in the review of the medical records. The impact of surveillance by medical records was 38.4% (36/96) in relation to the clue-based monitoring.

Conclusion: the surveillance by medical records, despite its acknowledged limitation, contributed in an important way to know, in fact, the rates of infection of the surgical site. It is suggested to the services of investigation of infections of the surgical site that the methods adopted for surveillance are rethought and, above all, that the rates obtained from different possible perspectives are validated.

DESCRIPTORS: Surgical wound infection. Epidemiological surveillance. Epidemiological surveillance services. Nursing.

VIGILÂNCIA POR PISTAS OU RETROSPECTIVA? QUAL O IMPACTO NA NOTIFICAÇÃO DAS INFECÇÕES DO SÍTIO CIRÚRGICO EM CIRURGIA CARDÍACA

RESUMO

Objetivo: avaliar o impacto das infecções do sítio cirúrgico notificadas pela vigilância por pistas comparadas àquelas detectadas pela avaliação retrospectiva do prontuário do paciente.

Método: estudo epidemiológico e de reflexão conduzido em um hospital de grande porte, público, universitário.

Resultados: a coleta dos dados ocorreu por meio de registros das notificações por pistas, realizada pela comissão de controle de infecção e por análise dos prontuários dos pacientes submetidos às cirurgias cardíacas entre os anos de 2011 e 2014. O diagnóstico da infecção do sítio cirúrgico seguiu os critérios definidos pelo National Healthcare Surveillance Network do Centers Disease Control. Os dados foram analisados no programa Epi-info® 6.4, por estatística descritiva. Foram analisados 294 pacientes submetidos a cirurgias cardíacas pela vigilância por pistas e 195 por revisão de prontuário. Notificaram-se 17 (65,9%) infecções do sítio cirúrgico superficiais; uma (3,8%) profunda; oito (30,8%) de órgão/cavidade na vigilância por pistas; 25 (69,4%) incisórias superficiais; dois (5,6%) profundas e nove (25%) de órgão/cavidade na revisão de prontuários. O impacto da vigilância por prontuários foi de 38,4% (36/96) em relação à vigilância por pistas.

Conclusão: a vigilância por prontuários, apesar de sua reconhecida limitação, contribuiu, de forma importante, para se conhecer, de fato, as taxas de infecção do sítio cirúrgico. Sugere-se, aos serviços de investigação das infecções do sítio cirúrgico, repensar os métodos adotados para vigilância e, sobretudo, validar as taxas obtidas sob diferentes perspectivas que lhe sejam possíveis.

DESCRITORES: Infecção da ferida cirúrgica. Vigilância epidemiológica. Serviços de vigilância epidemiológica. Enfermagem.
INTRODUCTION

Cardiac surgeries are among the most performed surgical procedures in the world, happening on an average of around 2,000 in the United States, 900 in Europe, and in Brazil, 350 for every 1,000,000 inhabitants per year.1-2

Despite the improvement in the quality of life of the person undergoing cardiac surgery, there is a risk of postoperative complications, including the surgical site infection (SSI), which is the most common problem for the surgical patient.3-4

The SSI stand out because they are among the main infections related to healthcare, causing great concern about the magnitude of its occurrence and reaching 31% among the hospitalized patients.5-6

In Brazil, the SSI are in the third position among all the infections in the health services, with rates ranging from 14% to 16% in hospitalized patients. And they are a consequence of the surgical manipulation, and can occur in different plans, ranging from the surgical incision, to manipulated organs/cavities.7-8

In cardiac surgeries, the SSI are a serious problem and have a great economic impact due to the prolonged hospitalization time, the cost with antimicrobial agents and to raise the mortality rate, even after treatment.3-9-11

However, the real knowledge of these devastating epidemiological aspects is only possible from the information obtained by the epidemiological surveillance of these patients. The epidemiological surveillance is an important tool for notifying infections in order to recognize their behavior, patient profile, associated morbidity and mortality and, consequently, to propose measures aimed at their prevention.7

The epidemiological surveillance of the SSI has been recommended by different methods such as active searches in patient records (prospective or retrospective) or by clues, from results of laboratory tests, positive cultures, prescription of antimicrobials or direct contact with professionals.7-8 However, it is evident in the daily practice that, for many reasons, many services have adopted the surveillance by clues without continuous and direct follow-up of the patient, which may lead to underreporting of the actual occurrence of infections. In view of the above, this study aims at evaluating the impact of the SSI reported by the prospective clue-based surveillance compared to those detected by the assessment of the patient’s medical records submitted to cardiac surgery.

METHOD

Cross-sectional study, carried out at a public university hospital in Minas Gerais, with 509 beds registered in the National Registry of Health Establishments for exclusive care to patients of the Unified Health System (SUS – “Sistema Único de Saúde”), after approval by the Research Ethics Committee, under CAAE-53843316.4.0000.5149.

In order to collect information, the infection control commission report was evaluated in relation to patients who underwent cardiac surgery in the period from January 1, 2011 to December 31, 2014 and who were notified with a diagnosis of SSI. And, in a complementary way, the evaluation of
the medical records of the patients submitted to the same surgery and in the same predetermined period was conducted. The patients who died less than or equal to 24 hours after surgery were excluded, whose surgical procedure was performed in another institution or who presented surgical indication due to infectious complications of previous procedures.

The review of the infection control commission report occurred shortly after its provision by the service, followed by an analysis of the medical records of the patients submitted to myocardial revascularization surgeries or valve prosthesis implantation in the services, occurring according to protocol of release by the service of medical and statistical filing.

The information collection was conducted by a nurse with experience in infection control in continuous activity for over twenty years in this service. A data collection instrument was used with items that included the presence and absence of SSI and the site affected (incisional superficial, deep incisional or organ/cavity); the use of antimicrobial; the laboratory results and the re-hospitalization or communication of the SSI by the surgeon of the case. In both sources of infection search, the National Healthcare Surveillance Network notification criteria of the Centers for Disease Control were adopted; and the case analysis was carried out by the main investigator, specialist in surveillance and control of hospital infections, with extensive experience in the area.

After gathering the data, the SSI rates obtained by the two methods were compared. The data were compiled into a database in the Epi-info® program, version 6.04, and the descriptive statistics was performed.

RESULTS

Through the analysis of the report issued by the institution’s surveillance service, 294 patients who underwent cardiac surgeries were identified, distributed between myocardial revascularization surgeries and heart valve implants, in the period from January 1, 2011 to December 31, 2014. Regarding the SSI notification, it occurred in 8.8% (26/294). The lowest annual rate was recorded as 3.9% in 2014; and the highest in 2013, with 34.6% for clue-based surveillance.

Through direct surveillance by medical record analysis, in the same period of the study, a total of 195 patients submitted to cardiac surgeries was identified, with a SSI rate of 18.5% (36/195). Similarly, the lowest annual infection rate was also in 2014, however, it was estimated to be 13.9, and the highest in 2011, with 30.6%.

It should be highlighted that the difference between the quantities of cardiac surgeries identified by the two methods of records for the analysis is justified by the occurrence of a fire in the medical record service of the study institution, which destroyed part of its archive in October 2014.

According to the site affected, in a global way, in the clue-based surveillance during the study period, 17 (65.4%) superficial SSI were reported; one (3.8%) deep and eight (30.8%) of organ/cavity, totaling 26 SSI. On the other hand, in the direct evaluation of the medical records, 25 (69.4%) superficial incisional SSI were counted; two (5.6%) deep and nine (25%) of organ/cavity, among the 36 SSI (Table 1).

The retrospective surveillance, through the medical records, accounted for an increase of 38.4% (36/26) in relation to the SSI, compared to the surveillance by analysis of the internal report of the surveillance service (by clues), being one deep incisor and nine superficial incisors, totaling ten other SSI cases. As for the affected structure, the impact to the superficial incisional site increased by 47% (25/17) and the deep incisional site by 50% (1/2).

Table 1 - Prevalence of Surgical Site Infection, according to the year of notification and type of epidemiological surveillance, prospective by clues (n=294) and retrospective analysis of the medical records (n=195), performed among patients submitted to cardiac surgery, from 2011 to 2014. Belo Horizonte - MG, Brazil, 2017.

| Type of epidemiological surveillance | Prospective surveillance by clues | Retrospective surveillance by medical records analysis |
|-------------------------------------|----------------------------------|------------------------------------------------------|
|                                     | Surgical Site Infection          | Total                                               |
|                                     | n SUP*                          | DEEP† ORG/CAV‡ | N | %  |
| 2011                               | 82                             | 04 01 03 | 8 | 9.8|
|                                     |                                 |                                                     | 62 | 07 02 02 | 11 | 22.9 |

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In order to analyze the same group of patients common to both types of registries and to verify if there would be difference in the SSI rates, as well as in the affected structure, a subsample of 155 patients was constituted. In this sub-sample, a rate of 11.6% SSI (18/155) was identified through the surveillance by clues, being 13 superficial incisors and 4 of organ and cavity. And, by review of the medical records, 16.8% (26/155) were reported (Table 2).

Table 2 - Prevalence of Surgical Site Infection, distributed per year, according to the type of epidemiological surveillance performed in the patients (n=155) submitted to cardiac surgery, from 2011 to 2014. Belo Horizonte, MG, Brazil, 2017.

| Year | Total patients | Type of epidemiological surveillance | Prospective surveillance by clues | Retrospective surveillance by medical records analysis |
|------|----------------|--------------------------------------|----------------------------------|------------------------------------------------------|
|      |                |                                      | N | %         | n | %         |
| 2011 | 49             |                                      | 3 | 6.1       | 7 | 14.3      |
| 2012 | 38             |                                      | 5 | 13.2      | 7 | 18.4      |
| 2013 | 43             |                                      | 9 | 20.9      | 9 | 20.9      |
| 2014 | 25             |                                      | 1 | 4         | 3 | 12        |
| Total| 155            |                                      | 18 | 11.6      | 26 | 16.8      |

There was an impact of 44.4% of SSI reported by the review of medical records compared to the notification by clues, being four superficial incisonal SSI by affected structure, one deep incisional and three of organ and cavity, if considered the same group assessed by the two methods.

DISCUSSION

The SSI surveillance is an important tool because it delineates the magnitude of these complications and their potential impact on the patient, the institution and the professionals, especially when evaluating the mortality associated with the cardiac surgery, which is estimated at around 8% to 20%.9,11-13

Studies that deal with the identification of the SSI rates in cardiac surgeries point to a significant variation in its occurrence, around 1.2% to 9.4%.9,14-15 This variation brings the difference between the diagnostic criteria adopted, the qualification of the surveillance team, the profile of the institution and the patient, but, above all, of the methods used.

The impact of the surveillance through the medical records analysis represented an increase of more than 38.4%, compared to that performed by clues, in a report issued by the hospital infection notification commission. Despite this, many criticisms are made to the surveillance by medical records analysis, which is considered a passive method, mainly due to its characteristic of not allowing direct actions of intervention during the hospitalization of the patient. On the other hand, the overload of activities of the professionals from the services responsible for surveillance has been increasing, whose ongoing demands for staff training, campaigns, audits, reporting, and systematic meetings/representations, in all institutional instances, have clearly left in the background the actions of direct follow-up of the patient.

Thus, over time, the work process of infection control professionals has evolved, with new care requirements in which global surveillance has been giving way to optimized methods, being progressively improved, aiming to rationalize the collection time, using diagnostic clues, computerizing the services, reducing the time spent in consolidating the data and seeking to allow the professional to invest more time in the interpretation of the report and in educational activities.16

However, the proactive approach to the occurrence of infection and the direct observation of patients, already restricted to those of critical units, were being left in the background, even if they were anchored in a speech that the clue-based surveillance would solve the issue of time management.
Nevertheless, the prospective surveillance through patient follow-up during hospitalization is recommended by national and international guidelines.\(^7\,8\) However, structural conditions and, above all, the quantity of human resources have played a mandatory role in defining the scope of action of the committees and surveillance services. No study has been found to show whether the changes that have been taking place over time have been able to meet to the institutional demands. Infection control professionals continue to be overburdened, many activities have been incorporated into their work, however, these activities have not reflected equally in improving the quality and knowledge of the epidemiology of hospital infections.

It is necessary, therefore, to highlight the fundamental aspects of healthcare, which are related to patient surveillance, especially at a time when one is ostensibly called to control outbreaks, to avoid the spread of bacterial resistance, to promote improvements in the care processes, aiming at the accreditation of institutions. But it is not encouraged to return to the bases of the epidemiological surveillance in order to know the distribution of events, their profile and impacts to promote effective actions.

A surveillance system will only be useful if it is able to detect trends in indicators, increase of cases and identify risk factors for certain groups.\(^7\,8\,16\)

In this study, it was evidenced that the retrospective medical record surveillance, despite its recognized limitations, was able to measure with a significant impact the SSI rates in cardiac surgeries in a proportion higher than 38%; and that when the denominators were adjusted in a sub-sample of the same patients, this impact remained clear and unequivocal, evidencing a 44.4% increase in the diagnosis of SSI.

Knowledge about the magnitude and impact of SSI in cardiac surgical patients is essential for the planning of prevention and control measures in order for them to be effective.

In this article, it was explored the relevance of the occurrence of SSI in one of the most performed surgical procedures: the cardiac surgery. It is important to emphasize that in this universe it is necessary to modify the perspective and the practice of health professionals, rethinking the methodologies used and their real impact on the actions performed in patients under care and for professionals who work in the services. It is also necessary to know how the events actually occur, with the purpose of basing the managers’ decision-making in health institutions and justifying the consolidation of the implementation of actions based on quality and safe healthcare.

Although the findings of this study are relevant, they should be interpreted from the difference obtained in the SSI notification in cardiac surgeries, which can also contribute to a design of the scenario for the prevention of SSI and for the adoption of safe conducts, in addition to contributing to deepen the discussion about the problematization of the surveillance methods adopted, their strengths and weaknesses.

**CONCLUSION**

The epidemiological surveillance is an important tool to identify the epidemiological profile of infections related to healthcare, among them, the SSI. The prospective clue-based surveillance is the one recommended by national and international guidelines; however, it presented an important limitation in the SSI notification in this study, when compared to the surveillance by medical records.

It is suggested that the services of infection control and notification may, from the results of this study, have subsidies to rethink the methods adopted for surveillance; and, above all, to validate the rates obtained from different possible perspectives. It also draws the attention of managers, due to the implication of human resources management in many demands.

To rethink the impacts of the indicators obtained by the adopted methods, in the case of the SSI, is a matter of perceiving the proposition of effective policies of patient, professional and institutional safety that allow to direct qualified practices that impact mainly on the cost and the on the care quality.

**REFERENCES**

1. Gelijns AC, Moskowitz AJ, Acker MA, Argenziano MA, Geller NI, Puskas JD et al. Management practices and major infections after cardiac surgery. J Am Coll Cardiol [Internet]. 2014 Jul [cited 2017 Oct 12]; 64(4):372-81. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4222509/

2. Mejia OAV, Lisboa LAF, Dallan, LAO, Pomerantzeff PMA, Moreiras LFP, Jatene FB et al. Validação do 2000 Bernstein-Parsonnet e EuroSCORE no Instituto do Coração – USP. Rev Bras Cir Cardiovasc [Internet]. 2012 [cited 2017 Oct 12]; 27(2):187-94. Available from: http://www.scielo.br/pdf/rbccc/v27n2/v27n2a05.pdf

3. Alasmari FA, Tleyjeh IM, Riaz M, Greason KL, Berbari EF, Virk A, et al. Temporal trends in the incidence...
of surgical site infections in patients undergoing coronary artery bypass graft surgery: A population-based cohort study: 1993 to 2008. Mayo Clin Proc [Internet]. 2012 Jul [cited 2017 Jan 20]; 87(11):1054-61. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3532679/

4. Nicolau JC, Timerman A, Marin-neto JA, Piegas LS, Barbosa CJDC, Franci A. Sociedade Brasileira de Cardiologia. Diretrizes da sociedade brasileira de cardiologia sobre angina instável e infarto agudo do miocárdio sem supradesnivel do segmento ST. Arq Bras Cardiol [Internet]. 2014 [cited 2017 Jan 20]; 102(33):1-61. Available from: http://publicacoes.cardiobr.com/consenso/2014/Diretriz_de_IAM.pdf

5. Magili SS, Hellinger W, Cohen J, Kay R, Bailey C, Boland B, et al. Prevalence of healthcare-associated infections in acute care hospitals in Jacksonville. Infect Control Hosp Epidemiol [Internet]. 2012 [cited 2017 Jan 20]; 3(3):283-91. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4648350/

6. Mafillii SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate Point-Prevalence Survey of Health Care–Associated Infections. N Engl J Med [Internet]. 2014 [cited 2017 Jan 20]; 370(13):1198-208. Available from: http://www.nejm.org/doi/pdf/10.1056/NEJMoai1306801

7. Agência Nacional de Vigilância Sanitária. Critérios Nacionais de Infeccões relacionadas à Assistência à Saúde–Sítio Cirúrgico. Brasília, Brasília (DF): Agência Nacional de Vigilância Sanitária, 2017.

8. Centers for Disease Control and Prevention. Surveillance Definitions for Specific Types of Infections. National healthcare safety Network (NHSN) Manual, Patient Safety Component Protocol. MMWR Recomm Rep [Internet]. Apr 2015 [cited 2017 Jan 15]: 1-25. Available from: https://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf?agree=yes&next=Accept

9. Jenks PJ, Laurent M, McQuarry S, Watkins R. Clinical and economic burden of surgical site infection (SSI) and predicted financial consequences of elimination of SSI from an English hospital. J Hosp Infect [Internet]. 2014 [cited 2017 Jan 10]; 86:24-33. Available from: http://www.journalofhospitalinfection.com/article/S0195-6701(13)00344-7/pdf

10. Kobayashi J, Kusachi S, Sawa Y, Motomura N, Imoto Y, Makuuchi H, et al. Socioeconomic effects of surgical site infection after cardiac surgery in Japan. Surgical Today [Internet]. 2015 [cited 2017 Jan 10]; 15:422-8. Available from: https://link-springer-com.ez27.periodicos.capes.gov.br/article/10.1007%2Fs00595-014-0969-2

11. Moraes AA, Abdou CS, Chammas AZ, Aguier YS, Mendes LC, Farsky PS. Mortalidade em longo prazo da infecção esternal profunda após cirurgia de revascularização do miocárdio. Rev Bras Cir Cardiovasc [Internet]. 2012 [cited 2017 Jan 10]; 27(3):377-82. Available from: http://www.scielo.br/pdf/rbccv/v27n3/v27n3a07.pdf

12. Chen L, Arduin JM, Sheng S, Muhlbaier L, Kanfani ZA, Harris AAD. Epidemiology and outcome of major postoperative infections following cardiac surgery: risk factors and impact of pathogen type. Am J Infect Control [Internet]. 2012 [cited 2017 Jan 10]; 40(10):963-8. Available from: http://www.sciencedirect.com/science/article/pii/S0196655312001125

13. Gualis J, Flórez S, Tamayo E, Álvarez FJ, Castrodeza J, Castaño M. Risk factors for mediastinitis and endocarditis after cardiac surgery. Asian Cardiovasc Thorac Ann [Internet]. 2009 [cited 2017 Jan 10]; 17(6):612-6. Available from: http://journals.sagepub.com.ez27.periodicos.capes.gov.br/doi/pdfs/10.1177/0218492309349071

14. Cossin S, Malavaud S, Jarno P, Giard M, L´Héritier, F, Simon L, et al. Surgical site infection after valvular or coronary artery bypass surgery: 2008-2011 French SSI national ISSO-RAISIN surveillance. J Hosp Infect [Internet]. 2015 [cited 2017 Jan 10]; 1-6. Available from: http://www.sciencedirect.com/science/article/pii/S0195670115002881

15. Mannijn J, Wille JC, Kloeck J, Benthem BHB. Surveillance and epidemiology of surgical site infections after cardiothoracic surgery in the Netherlands, 2002-2007. J Thorac Cardiovasc Surg [Internet]. 2011 [cited 2017 Jan 10]; 141(4):899-904. Available from: http://www.sciencedirect.com.ez27.periodicos.capes.gov.br/science/article/pii/S0022522310011219

16. Mocanu V, Buth K, Johnston LB, Davis I, Hirsch GM, Légère J. The importance of continued quality improvement efforts in monitoring hospital-acquired acquired infection rates: a cardiac surgery experience. Ann Thorac Surg [Internet]. 2015 Jun [cited 2017 Oct 10]; 99(6):2061-9. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25795297