Original article

Temporal trends of healthcare associated infections and antimicrobial use in 2011-2013, observed with annual point prevalence surveys in Ferrara University Hospital, Italy

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Keywords

Healthcare-associated infections • Antimicrobial use • Point prevalence surveys

Summary

Introduction. *Healthcare associated infections (HAIs) and misuse of antimicrobials (AMs) represent a growing public health problem. The Point Prevalence Surveys (PPSs) find available information to be used for specific targeted interventions and evaluate their effects. The objective of this study was to estimate the prevalence of HAIs and AM use, to describe types of infections, causative pathogens and to compare data collected through three PPSs in Ferrara University Hospital (FUH), repeated in 3 different years (2011-2013). The population-based sample consists of all patients admitted to every acute care and rehabilitation Department in a single day.*

Methods. *ECDC Protocol and Form for PPS of HAI and AM use, Version 4.2, July 2011. Risk factor analysis was performed using logistic regression.*

Results. *1,239 patients were observed. Overall, HAI prevalence was 9.6%; prevalence was higher in Intensive Care Units; urinary tract infections were the most common HAIs in all 3 surveys; E.coli was the most common pathogen; AM use prevalence was 51.1%; AMs most frequently administered were fluoroquinolones, combinations of penicillins and third-generation cephalosporins. According to the regression model, urinary catheter (OR: 2.5) and invasive respiratory device (OR: 2.3) are significantly associated risk factors for HAIs ($p < 0.05$).*

Conclusions. *PPSs are a sensitive and effective method of analysis. Yearly repetition is a useful way to maintain focus on the topic of HAIs and AM use, highlighting how changes in practices impact on the outcome of care and providing useful information to implement intervention programs targeted on specific issues.*

Introduction

Healthcare associated infections (HAIs) represent a growing public health problem in terms of patient safety and economic burden [1-3]. The Center for Disease Control (CDC) estimates the increased mean length of hospital stay for each HAI to be 7 extra days, ranging from 1-4 days for urinary tract infections (UTIs) to 7-30 days for pneumonia (PN). In Europe, HAIs cause 16 million additional days of hospitalization per year, 37,000 related deaths and 7 billion euros of additional costs (direct costs only) [4]. The Italian National Health Institute estimates 450,000-700,000 HAIs per year in Italian hospitals, 30% of which could be prevented; HAIs could be directly responsible for 1,350-2,100 avoidable deaths per year [5]. Misuse of antimicrobials (AMs) is a growing public health problem worldwide, associated with an increase in drug resistant microorganisms and adverse drug reactions that generate huge economic costs [6, 7].

The implementation of surveillance systems for both HAI and AM use is a relevant topic in modern public health [8, 9]. Although continuous surveillance still represents the gold standard for infection control, it requires a huge amount of human and economic resources but has rarely been used in multicenter studies. Instead, Point Prevalence Surveys (PPS), despite their inherent limitations in terms of accuracy of results and possibility of bias, are a highly feasible alternative, easier to perform even on large scale multicenter studies, less expensive and less time consuming. PPSs offer many benefits, including easy repeatability and the ability to provide meaningful information to be used for specific targeted interventions. The introduction of standardized protocols such as the European Center for Disease Control (ECDC) Protocol for PPS of HAI and AM use in acute care hospitals, version 4.2 2011-2012 [10], guarantees consistency of results and easy repeatability. Results of local surveys may also be used for yearly intra-hospital

comparison or benchmarking at regional, national or international level. In Ferrara University Hospital (FUH), infection and AM stewardship by PPS began in 1992, with a local Protocol and data entry form, updated over the years in agreement with the literature references [11]. This Protocol was used until 2011, when FUH participated in the first full scale ECDC PPS, October 2011.
The survey was repeated in 2012 and 2013. Objectives of these studies were: to estimate the overall burden of HAIs and use of AMs in the FUH; to describe HAIs and AM use by type of functionally homogeneous wards; to allow a comparison of data collected during three surveys and with Italian and European data.

Methods

The surveys took place in October 2011, November 2012 and November 2013 in the FUH, a tertiary care hospital with 857 beds in 2011 and, after moving to a new hospital in 2012, with 711 beds. The materials and tools developed for the ECDC PPS of HAI and AM use in acute care hospitals were used for these surveys: the PPS protocol and codebook v4.2, including the case definitions of HAI, PPS data entry forms in an editable format for translation purposes, PPS hospital software HELICSWin.net, User manual – PPS hospital software HELICSWin.net [10]. All acute wards were included, except for Day-surgery and Day-Hospital departments. The study included all patients admitted to the ward before or at 8 a.m. and not discharged from the ward at the time of the survey, including neonates, if born before/at 8 a.m. For each ward, data had to be collected in a single day. Data collection for each survey was completed in two weeks. The surveys were carried out by trained medical doctors of the Postgraduate School of Hygiene and Preventive Medicine of Ferrara University, supported by doctors and nurses of the Hospital Network for Infection Control of each ward. The ECDC standard "Patient data form" was used, structured according to the following sections: demographic data, admission data, clinical data, AM use and HAI data [10].
Demographic, admission and clinical data, useful for identifying patient-based denominator data and risk factors, included: ward name, survey date, patient counter, age, sex, date of admission, surgery since admission, McCabe score [12], invasive devices in place on survey date (central vascular catheter-CVC, peripheral vascular catheter-PVC, urinary catheter, intubation). Only any active HAI on the survey date was recorded on the form [10].
Data collected for HAI included: presence of a relevant invasive device before onset (intubation for PN, central vascular catheter / peripheral vascular catheter for bloodstream infection-BSI and urinary catheter for UTI) [13], HAI present at admission, date of onset, origin of infection (if bloodstream infection, source) and microorganisms data.
AM data (including generic or brand name, route, indication, diagnosis/site of infection, reason) were collected when a patient was receiving an AM on the day of survey (or in the 24 hours before the day of the survey for surgical prophylaxis). Registered drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification [14]. AMs included in the survey were Anatomical Therapeutic Chemical classes J01 (antibacterials), J02 (antifungals) and J04 (antimycobacterials). Indication for use of systemic AMs was recorded according to the following classification: community-acquired infection, infection acquired in long-term care facility (e.g. nursing home) or chronic-care hospital, acute hospital acquired infection, surgical prophylaxis (single dose, one day, more than one day), medical prophylaxis, other indications, unknown indication/reason, unknown/missing information on indication not verified during survey [10]. Data were collected using the standard ECDC software HELICSWin.net v. 1.3. Statistical analysis was performed using Stata v.13. Difference in the distribution of nominal variables was assessed using Pearson's chi-square test with significance level set at 0.05. Continuous variables were tested for normality of distribution both graphically and by means of Shapiro-Wilkinson test, difference in distribution was then tested using Kruskal-Wallis test. Prevalence rate of HAI was calculated as the percentage of infected patients over the total number of patients observed during each survey. AM use prevalence was calculated as the percentage of the number of patients receiving at least one AM over the total number of patients observed. Risk factors analysis were performed by means of logistic regression in relation to two outcomes: presence of at least one HAI and receipt of at least one AM.
Continuous variables were recoded into categories in order to maintain consistency with ECDC PPS [15] and to address the influence of outliers. The final models for both outcomes were developed by adding those risk factors which resulted to be significant ($P < 0.2$) in univariate analysis in a forward stepwise manner [16]. Significance level for inclusion in final model was set at $p < 0.05$. The presence of a central vascular catheter or peripheral vascular catheter was excluded from both models because of the correlation with the parenteral administration of AMs. Presence of relevant invasive devices was considered before the onset of an HAI for the HAI regression model. Length of stay in the HAI model was considered until the date of HAI onset if an HAI occurred during current hospital stay. Goodness-of-fit was assessed on eight smaller random sub-samples of the data using the Hosmer–Lemeshow chi square test. The discriminatory accuracy of the multiple logistic regression models was assessed using receiver operating characteristic (ROC) analysis. Standardized prevalence rates were calculated by using a 2-step method which takes into consideration predicted probabilities of the outcome according to the regression model and indirect standardization. The predicted probabilities were used to determine the mean predicted risk of HAI or AM use for each survey. Risk index ratios were calculated by dividing the observed (unadjusted) prevalence rates by the mean predicted risk of each survey, and adjusted prevalence rates

were determined by multiplying standardized ratios by the observed prevalence rates in the entire study sample.

Results

Overall, 1,239 patients were observed in the three surveys; the mean age was 62.6 years and 47.3% were male. Mean length of stay was 9.4 days (median 6 days). At the time of survey, a central vascular catheter was present in 20.2% of observed patients; a peripheral vascular catheter in 56.0%; a urinary catheter in 35.9% and the percentage of mechanically ventilated / intubated patients was 3.8%. Differences among data collected during the three surveys proved to be statistically significant ($p < 0.05$) for: presence of peripheral line, presence of central line, McCabe score and surgery since admission. The overall prevalence of HAI was 9.6%, with a total number of 49 HAIs in 2011, 37 in 2012, and 54 in 2013 (HAIs to patients ratio: 1.1 in 2011, 1.1 in 2012, 1.3 in 2013). Case-mix corrected prevalence rates were: 10.1% for 2011, 8.9% for 2012 and 9.6% for 2013. UTIs were the most common HAI in all three surveys, followed by PN (in 2011 and 2012) and bloodstream infections in 2013 (Tab. I). A total of 82.8% HAIs originated in the current hospital. Regression analysis of risk factors associated with the onset of at least one HAI shows statistical significance for: length of stay at risk 4-7 days (OR: 1.9, 95%CI 1.1-3.4; $p = 0.030$), length of stay at risk 8-14 days (OR: 2.3, 95%CI 1.2-4.3; $p = 0.010$) and length of stay at risk > 3 weeks (OR: 3.8, 95%CI 2.1-7.1; $p < 0.001$); McCabe score "Rapidly fatal disease" (OR: 2.4, 95%CI 1.5-3.8; $p < 0.001$); use of urinary catheter (OR: 2.5, 95%CI 1.6-3.7; $p < 0.001$); mechanical ventilation (OR: 2.3, 95%CI 1.1-4.5; $p = 0.023$). The prevalence of HAI was higher in Intensive Care Units in all three surveys.

At the time of the surveys, results for microbiological investigation were available for 120 HAIs (85.0%). *Escherichia coli* was the most common pathogen, followed by *Klebsiella pneumoniae* and *Enterococcus faecalis* (Tab. II). *Escherichia coli* was the most prevalent pathogen even when stratifying by survey and also the most frequent causative pathogen for UTI. During the 3-year study period, isolated strains of *Escherichia coli* were frequently third-generation cephalosporin resistant (range 10%-20%), but only in 2011 were they also carbapenem resistant. In 2011, 33.3% of *Klebsiella pneumoniae* strains were third-generation cephalosporin resistant and 16.7% were carbapenem resistant. Overall, the AM use prevalence was 51.1% (at least one AM). A total of 858 AMs were administered (Tab. III). Parenteral administration was the most prevalent route (69.0% in 2011, 74.0% in 2012 and 79.3% in 2013). AMs were mainly administered for treatment of an infection (relative frequency 61.0% in 2011, 56.2% in 2012 and 70.7% in 2013) and among these mainly for treatment of community acquired infections (57.6% in 2011, in 2012 59.1%, in 2013 60.1%). Surgical prophylaxis was mostly prescribed for more than one day (relative frequency: 65.4% in 2011, 72.0% in 2012 and 88.9% in 2013). Single dose prophylaxis was prescribed in 23.1% in 2011, 20.0% in 2012 and 11.1% in 2013 (relative frequency). One-day surgical prophylaxis was the least frequently prescribed. Prescription for medical prophylaxis was 19.8% in 2011, 24.9% in 2012, 15.0% in 2013. Considering all three surveys, antibacterials for systemic use (ATC group J01) accounted for 93.7% of all prescriptions. AMs most frequently administered were: J01MA fluoroquinolones (21.7% in 2011, 23.0% in 2012, 21.8% in 2013), J01CR combinations of penicillins including beta-lactamase inhibitors (20.4% in 2011, 19.2% in 2012, 21.8% in 2013), J01DD third-generation cephalosporins (22.7% in 2011, 16.6% in 2012, 16.8% in 2013). Fluoroquinolones were the most commonly used AMs in symptomatic lower UTI (total 28.8%) and PN (total 24.5%), including both community acquired infections and HAI. Risk

Tab. I. Characters of Healthcare associated infections (HAIs).

HAI data	Year of survey		
	2011 (N = 450[a])	2012 (N = 379)	2013 (N = 407)
HAI Prevalence (at least one HAI) %	10.0	8.7	10.1
Total number of HAIs	49	37	54
Infection Site - No. (%) of HAI by year of survey:			
Urinary tract infections	18 (36.7)	9 (24.3)	22 (40.7)
Pneumonia	7 (14.3)	9 (24.3)	6 (11.1)
Bloodstream infections (BSI)	5 (10.2)	2 (5.4)	10 (18.5)
Surgical site infections	4 (8.2)	4 (10.8)	3 (5.6)
Gastro-intestinal system infections	5 (10.2)	2 (5.4)	2 (3.7)
Other lower respiratory tract infections	2 (4.1)	1 (2.7)	2 (3.7)
Catheter-related infections w/o BSI		2 (5.4)	
Other	8 (16.3)	8 (21.6)	9 (16.7)

[a] 3 missing records excluded

Tab. II. Top five microorganisms isolated in healthcare-associated infections and percentage of antimicrobial resistance markers.

Microorganisms	No. of isolated microorganisms by year of survey		
	2011 (N = 74)	2012 (N = 28)	2013 (N = 73)
Escherichia coli (%C3G-R) (%Car-R)	24 (16.7) (16.7)	10 (20.0) (0.0)	20 (10.0) (0.0)
Klebsiella pneumoniae (%C3G-R) (%Car-R)	6 (33.3) (16.7)	4 (0.0) (0.0)	6 (0.0) (0.0)
Enterococcus faecalis	2	5	5
Candida albicans	5		6
Staphylococcus epidermidis	1	1	6

C3G-R, Third-generation cephalosporin resistance

Car-R, Carbapenem-resistant

Tab. III. Characters of Antimicrobials (AMs).

AM use data	Year of survey		
	2011 (N = 450[a])	2012 (N = 379)	2013 (N = 407)
AM use prevalence (at least one AM) %	54.4	50.1	48.4
Total number of AM	313	265	280
Top ten antimicrobials agents (ATC codes) - No. (%) of AM by year of survey:			
J01MA Fluoroquinolones	68 (21.7)	61 (23.0)	61 (21.8)
J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	64 (20.4)	51 (19.2)	61 (21.8)
J01DD Third-generation cephalosporins	71 (22.7)	44 (16.6)	47 (16.8)
J01GB Aminoglycosides	13 (4.2)	17 (6.4)	17 (6.1)
A07AA Intestinal anti-infectives antibiotics	7 (2.2)	3 (1.1)	2 (0.7)
J01DB First-generation cephalosporins	23 (7.3)	11 (4.2)	6 (2.1)
J01DH Carbapenems	9 (2.9)	11 (4.2)	20 (7.1)
J01XA Glycopeptide antibacterials	11 (3.5)	16 (6.0)	13 (4.6)
J01XD Imidazole derivatives	7 (2.2)	8 (3.0)	13 (4.6)
J02AC Triazole derivatives	9 (2.9)	10 (3.8)	7 (2.5)
J01FA Macrolides	12 (3.8)	9 (3.4)	4 (1.4)

[a] 3 missing records excluded
ATC, Anatomical Therapeutic Chemical

factors associated with administration of at least one AM showing statistical significance in the regression model were: patient located in surgical ward (OR: 1.7, 95%CI 1.1-2.7; p = 0.010) and Intensive Care Unit (OR: 2.7, 95%CI 1.2-6.0; p = 0.015); length of stay 4-7 days (OR: 1.4, 95%CI 1.1-1.9; p = 0.016); length of stay 8-14 days (OR: 1.6, 95%CI 1.1-2.2; p = 0.010); patient underwent non-NHSN/minimal surgery during current hospitalization (OR: 1.5, 95%CI 1.1-2.2; p = 0.013); use of urinary catheter at the time of survey (OR: 1.9, 95%CI 1.4-2.4; p < 0.001); mechanical ventilation at the time of survey (OR: 2.6, 95%CI 1.1-6.0; p = 0.030). Case-mix corrected AM use prevalence rates were: 54.2% in 2011, 50.5% in 2012 and 47.9% in 2013.

Discussion

The described prevalence rate of nosocomial infections was higher than the values reported in other studies [17-21] including the ECDC's 2011 report [15], which estimates a prevalence rate of 6.0% (country range 2.3%–10.8%) in European acute-care hospitals (6.1% in Italy). This difference in the reported values is due in part to the different characteristics of the hospitals included in the European survey which collects results from primary, secondary, tertiary care and specialized hospitals in different countries. However, the prevalence rate of HAI in FUH remains higher even when comparing results from tertiary care hospitals only (7.2%). One possible reason may be the fact that the surveys were carried out by independent auditors, to avoid conflicts of interest and to ensure the integrity of the auditing process. As confirmed by existing literature, Intensive Care Units were the most affected wards [15, 17-21]. UTIs were the most common HAI in all three surveys in FUH, unlike what is reported in other studies where PN and surgical site infections were more prevalent [15, 17, 18]. Use of urinary catheter, a well known risk factor for UTIs [22-24], was higher than what is reported in the literature [15, 19, 21]. Prevalence of surgical site infections was found to be lower than what is reported by other similar surveys [15, 17-21]. Appropriate urinary catheter indication is certainly an area which requires further analysis to assess possible overuse and guide practical interventions [25]. Year by year comparison of nosocomial infections and risk factors in the three surveys delivers substantially constant results even when corrected for case-mix by means of logistic regression. Risk factor analysis is consistent with data in the literature [15, 19, 21]. Statistically significant risk for HAI occurrence is independently associated with increased length of stay, McCabe Score "Rapidly fatal disease", use of urinary catheter and mechanical ventilation. Mechanical ventilation associated risk suggests a need for more effective preventive measures against ventilator-associated infections [26]. At the time of the surveys, results for microbiological investigation were available for 120 HAIs (85.0%). *Escherichia coli* was the most frequent microorganism isolated in all three surveys and the most frequent causative pathogen for UTI, followed by *Klebsiella pneumoniae*, *Enterococcus faecalis* and *Candida albicans*. These results show a higher prevalence of *Enterobacteriaceae* when compared with the ECDC's report data [15] which can be explained by the higher frequency of UTIs in FUH. AM use rates were higher than those reported in the literature [15, 19], while the average number of AMs to treated patients ratio is consistent with the value reported by ECDC [15], showing no evidence of a higher rate of multidrug protocol prescriptions in FUH. Fluoroquinolones, third-generation cephalosporins and combinations of penicillins (including beta-lactam inhibitors) were the most frequent AM prescribed in all three surveys, a similar result to other literature reports which further underline a widespread use of broad spectrum antibiotics combined in multidrug protocols that is often necessary to counteract the increasing prevalence of AM resistance [15, 17-19, 27]. On the other hand, the excessive and inappropriate use of antibiotics is the prime mover of the rapidly increasing prevalence of antibiotic-resistant microorganisms [28, 29]. AMs were mainly prescribed to treat an infection (mainly community acquired). Medical prophylaxis was the second most frequent indication in all three surveys. These results are similar to those reported by the ECDC's 2011 point prevalence survey for Italy [15]. Surgical prophylaxis was mostly prescribed for more than one day, while one-day surgical prophylaxis was the least frequently prescribed. These results are substantially similar to those reported by ECDC for Italy in 2011 and other similar studies [15, 18, 19], underlining that antibiotics are used for longer than what is suggested by the international consensus [30], further stressing the need for specific stewardship programs [31, 32]. Year by year analysis shows a decreasing, although not statistically significant, prevalence of AM prescription in FUH, dropping from 54.4% in 2011 to 48.4% in 2013, a result confirmed by standardization through logistic regression model. AM stewardship is a critical area of intervention in FUH, aimed at changing prescribing practices, leading to a better control of drug resistant microorganisms, improved appropriateness of antibiotic use and decreased costs.

Conclusions

FUH has a long history of activities aimed at risk management and infection control, based on a multimodal and multidimensional approach [11]. Moreover, the hospital's infection control policy includes: audit and feed-back to improve compliance of the healthcare workforce to good practices; retraining courses and educational programs; drafting reminders to support good practices for workers, patients and caregivers; continuous surveillance of surgical site infections; active support for the WHO Campaign "Save lives: clean your hands" since 2006, with the participation as an international site in the experimentation of WHO Guidelines on Hand Hygiene in Health Care (Advanced Draft) [33, 34]. Despite their limitations, PPS are not expensive, take little time to carry out and need few human resources. PPS are easy repeatable and provide meaningful information to use for specific targeted interventions. The yearly repetition will be a useful means of keeping interest alive on the subject of HAI and AM use [35] and highlighting how changes in healthcare practices affect outcome variables.

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Authors' contributions

PA, GG, AS, MCM was responsable for the research coordination and contributed to the protocol definition, data collection, data analysis, manuscript drafting and critical revision of the manuscript. BB, AV, AF contributed to the data collection, data analysis and critical revision of the manuscript. All authors read and approved the final manuscript.

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