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Major article

Relative frequency of health care-associated pathogens by infection site at a university hospital from 1980 to 2008

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Key Words:
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Background: We describe the relative frequency of health care-associated pathogens by infection site over 29 years using hospital-wide surveillance data from a large academic hospital.

Methods: Comprehensive hospital-wide surveillance was provided by trained infection preventionists using Centers for Disease Control and Prevention definitions. Five 5-year blocks and one 4-year block were created for each site: bloodstream infections (BSI), urinary tract infections (UTI), respiratory tract infections (RTI), and surgical site infections (SSI). The blocks of relative frequency of health care-associated pathogens were compared by χ^2 analysis, and trends for each pathogen were estimated by regression analysis.

Results: At least 1 pathogen was isolated from 28,208 (83.5%) of 33,797 health care-associated infections (HAI). *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Enterococcus* species, and *Clostridium difficile* and other anaerobes significantly increased, whereas *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* species, *Enterobacter* species, and other streptococci significantly decreased in the relative proportion of pathogens during the study period. By infection site, results showed significant increasing trends of *S aureus* in UTI, RTI, and SSI; CoNS in BSI and SSI; *Candida* in SSI; and *Enterococcus* in BSI and UTI.

Conclusion: Significant changes in relative frequency of health care-associated pathogens by infection site occurred over the 29-year period. These findings have implications for implementation of infection prevention strategies.

Health care-associated infections (HAI) are one of the most common adverse events threatening patient safety. HAI are estimated to be one of the top 10 causes of death in the United States.[1] According to the Centers for Disease Control and Prevention (CDC), approximately 1.7 million HAI and 99,000 HAI-related deaths occur each year in the United States.[2] From 1975 to 1995, the overall incidence of HAI in the United States reported to the National Nosocomial Infections Surveillance System (NNIS) has increased by 36%.[3]

Information about the relative frequency of isolated pathogens from HAI cases by infection site has implications for the implementation of infection control and prevention strategies. The National Healthcare Safety Network (NHSN) data from 2006 to 2007 reported the top 10 commonly isolated pathogens as follows: coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, *Enterococcus* species, *Candida* species, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterobacter* species, *Acinetobacter baumannii*, and *Klebsiella oxytoca*.[4] The spectrum of health care-associated pathogens may have changed over time following increased use of broad-spectrum antibiotics and invasive procedures and increasing numbers of immunocompromised patients.[5] Although national data on commonly isolated pathogens have been reported by the NHSN, the frequency of these reported pathogens cannot be compared over time because the participating NHSN hospitals are not randomly selected and do not consistently participate over time and therefore do not represent a well-defined

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cohort, which is a designated population traced over time.[6] For this reason, we reviewed the relative frequencies of health care-associated pathogens isolated in our institution during almost 3 decades, from 1980 to 2008.

METHODS

All data for pathogens associated with HAI during 1980 to 2008 were extracted from the University of North Carolina Health Care (UNCHC) electronic epidemiology database. HAI data including pathogen information have been collected since 1978 through comprehensive hospital-wide surveillance by trained full-time infection preventionists at UNCHC, currently an 800-bed teaching facility. HAI were determined based on the CDC's NNIS and NHSN case definitions,[7] with 2 exceptions: diagnosis of lower respiratory tract infection required chest radiography with an infiltration (even prior to the requirement by NHSN); bacteriuria required signs and symptoms of infection (ie, asymptomatic bacteriuria was not considered a UTI).[8] Otherwise, all updates to NNIS/NHSN case definitions were adopted. Separate codes for methicillin-resistant *S aureus* (MRSA) and vancomycin-resistant *Enterococcus* were introduced in 1996 to distinguish from susceptible *S aureus* and susceptible *Enterococcus.*

Based on the previous study from the same facility,[5] pathogens were categorized into 18 groups of related species. For frequency analysis of isolated pathogens by infection site, all cases regardless of device utilization were classified into 5 major categories: bloodstream infections (BSI), urinary tract infections (UTI), respiratory tract infections (RTI), surgical site infections (SSI), and other sites (eg, endocarditis, osteomyelitis, meningitis) as specified by NNIS/NHSN definitions.

To analyze the relative frequencies of pathogens isolated during 29 years, 6 time blocks were created (ie, five 5-year blocks and one 4-year block), and noninformative data such as "no growth" and "mixed flora" were deleted. To compare the relative frequency of isolated hospital-associated pathogens by time blocks, χ^2 tests were conducted using SAS version 8.2 (SAS Institute, Cary, NC). For trend analysis, logistic regression analysis was conducted across the 6 time blocks, and overall relative percentage change was calculated across the entire linear trend (from the first time block to the last time block) using the slope and intercept values. Significance for these multiple comparisons was set at $P < .003$ (Bonferroni correction, 0.05/17). Additional analyses of the yearly proportions and the actual number of isolates were conducted to aid in the interpretation of the relative frequency trend.

RESULTS

Overall, at least 1 pathogen was isolated from 28,208 (83.5%) of the 33,797 HAI during 29 years. In total, 35,510 pathogens were isolated from these 28,208 HAI (mean number of pathogens per HAI, 1.26). For the remaining 5,589 HAI, no pathogens were isolated, and infections were classified based on clinical criteria alone as specified by NNIS/NHSN definitions. The probability of isolating a pathogen differed by site as follows: urinary tract, 98.8%; respiratory tract, 75.5%; surgical site, 81.8%; and other, 68.8%. The probability of isolating a pathogen in the blood differed over time (1980 to January 1999, 99.9% vs February 1999 to 2008, 82.0%) because, after February 1999, all pathogens for secondary bloodstream infections were recorded as "no growth" even if a pathogen was isolated to avoid duplicate reporting of the same pathogen.

The overall relative frequency of pathogens by time blocks is displayed in Table 1. In total, the top 5 pathogens were *S aureus*, *E coli,* CoNS, "*Candida* and other yeasts," and *Enterococcus* species during 29 years, accounting for a total of 54.8% of all pathogens. The trend analyses showed significantly increasing relative frequency trends (Fig 1) with gram-positive cocci (*S aureus*, CoNS, and *Enterococcus* species) and significantly decreasing trends (Fig 2) with gram-negative bacilli (*E coli*, *P aeruginosa*, *Klebsiella* species, and *Enterobacter* species). The most dramatic change in health care-associated pathogens was the marked increase in infections with *S aureus*, and, from 1990 to 2008, *S aureus* was the most predominant pathogen in relative frequency (data not shown). Since a separate code for MRSA was introduced in 1996, the relative proportions of MRSA among *S aureus* HAI cases remained relatively constant from 55.9% to 44.4%.

Clostridium difficile, an emerging health care-associated pathogen, was categorized to "*C difficile* and other anaerobes" which had a 10th relative frequency ranking. We observed that, since 1987, *C difficile* comprised most of the proportion for the "*C difficile* and other anaerobes" category (data not shown). From 1995 to 2008, "*C difficile* and other anaerobes" showed a 4.0% increase from 1.5% to 5.5% in relative frequency.

The overall significant percent change of relative frequency of pathogens is summarized in Table 2. Among BSI, CoNS and *Enterococcus* species were significantly increased, whereas *E coli, Enterobacter* species, *P aeruginosa*, "*C difficile* and other anaerobes," *Klebsiella* species, and "*Candida* and other yeasts" were significantly decreased in relative frequency during 1980 to 2008. The most prominent relative frequency change in isolated pathogens from BSI was CoNS, which increased suddenly as an overwhelming predominant pathogen since 1995 (data not shown). Among UTI, *Enterococcus* species and *S aureus* showed significantly increasing trends, whereas *E coli and P aeruginosa* showed significantly decreasing trends in relative frequency. For the period of 2000-2004, "*Candida* and other yeasts," which did not show a significant change in the trend analysis, surpassed *E coli* as the proportional leading pathogen for UTI (ie, "*Candida* and other yeasts," 22.0% vs *E coli* 19.6%; data not shown). Although a significantly increasing trend for *Enterococcus* species was also observed across the time blocks, vancomycin-resistant *Enterococcus* contributed a relatively low frequency (<2%) to UTI. Among RTI, *S aureus* increased significantly, whereas *Klebsiella* species, *Enterobacter* species, *E coli*, and other streptococci decreased. Among SSI, *S aureus* and "*Candida* and other yeasts" showed significantly increasing trends, whereas *P aeruginosa*, *Klebsiella* species, *Enterobacter* species, and "*C difficile* and other anaerobes" decreased significantly in relative frequency. Over the time period, *S aureus* dramatically doubled (15% to more than 30%) in relative frequency as a predominating pathogen of both RTI and SSI.

DISCUSSION

This study is unique in that we were able to perform analyses on the relative frequency of pathogens isolated from HAI over almost 3 decades at a single hospital. Over the study time period, our hospital conducted comprehensive surveillance using standardized CDC case definitions by trained infection preventionists with low staff turnover. Although NNIS/NHSN did not recommend that participating hospitals perform hospital-wide surveillance after 1986 and most adopted a targeted surveillance method (eg, intensive care unit only, device-related infections),[8] our hospital maintained a comprehensive hospital-wide surveillance program for the entire time period. Comparable studies that provide relative frequency of pathogens hospital-wide and for an extended time period are lacking. Although the NHSN does periodically report data on frequency of health care-associated pathogens, these data are limited in that they cannot be compared over time because the participating NHSN hospitals do not represent a true or well-defined cohort[7] and are not a random selection of hospitals in the United States.

Table 1
Changes in relative frequency of health care-associated pathogens by time blocks from 1980 to 2008

	Total (1980-2008)			Percent of each time blocks						Trend analysis	
Organism	Rank	No.	%	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2008	% Change	*P* value
Staphylococcus aureus	1	5,483	15.4	11.8	11.2	16.0	18.2	17.3	15.5	5.3	<.0001
Escherichia coli	2	3,753	10.6	12.6	12.7	11.3	9.2	8.2	11.5	−3.1	<.0001
Coagulase negative staphylococci	3	3,587	10.1	6.9	7.6	8.1	12.7	13.2	9.2	4.8	<.0001
Candida and other yeasts	4	3,494	9.8	7.7	10.4	11.0	10.3	11.1	8.1	3.0	.1890
Enterococcus spp	5	3,138	8.8	8.1	5.8	8.0	8.8	10.2	10.7	3.8	<.0001
Pseudomonas aeruginosa	6	2,954	8.3	9.5	9.5	9.7	8.6	6.7	7.1	−3.1	<.0001
Klebsiella spp	7	2,186	6.2	7.3	7.7	5.9	6.3	4.9	5.7	−2.4	<.0001
Enterobacter spp	8	2,097	5.9	7.2	8.2	6.3	4.8	4.7	5.7	−2.7	<.0001
Other streptococci	9	1,252	3.5	5.0	4.1	2.8	3.6	3.1	2.9	−1.8	<.0001
Clostridium difficile and other anaerobes	10	1,044	2.9	3.3	3.2	2.9	1.5	1.9	5.5	0.8	.0025
Proteus spp	11	946	2.7	5.4	3.9	2.1	1.6	1.9	2.1	−1.8	<.0001
Serratia spp	12	802	2.3	3.8	2.5	2.1	1.8	2.1	1.7	0.8	<.0001
Acinetobacter spp	13	593	1.7	1.2	1.4	2.2	1.4	2.1	1.6	−1.5	.0163
Haemophilus spp	14	494	1.4	1.6	2.5	2.2	1.1	0.9	0.8	−2.0	<.0001
Bacteroides spp	15	349	1.0	2.6	1.6	1.0	0.3	0.4	0.7	−0.8	<.0001
Citrobacter spp	16	325	0.9	1.1	1.1	0.9	0.8	0.9	0.8	0.5	.0488
Group B streptococci	17	324	0.9	1.4	1.3	1.1	0.5	0.6	0.9	−0.3	<.0001
Other	18	2,689	7.6	3.5	5.2	6.2	8.5	10.0	9.5	6.7	<.0001
Total (n)		35,510		5,217	4,336	4,904	6,964	7,999	6,090		

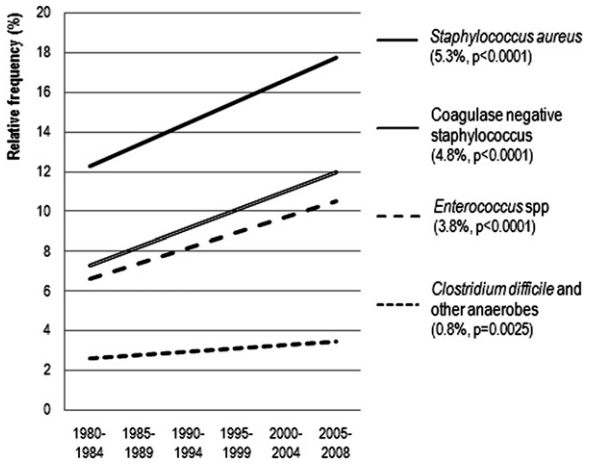

Fig 1. Pathogens with significantly increasing linear trends of relative frequency among top 10 pathogens from all health care-associated infections, 1980-2008. Note: legend, pathogen name (overall relative frequency change, *P* value).

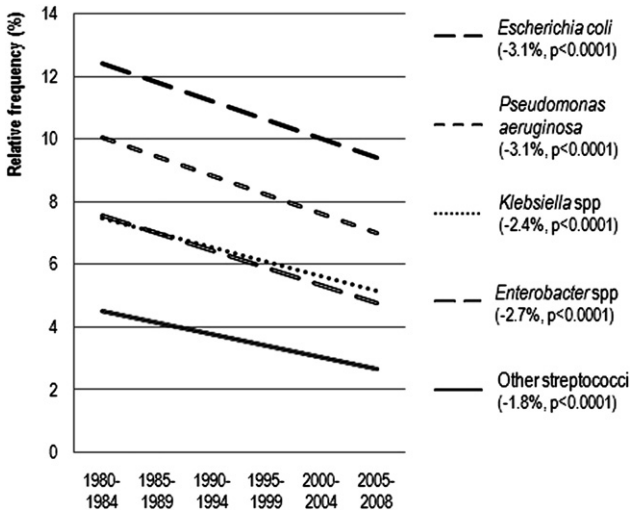

Fig 2. Pathogens with significantly decreasing linear trends of relative frequency among top 10 pathogens from all health care-associated infections, 1980-2008. Note: legend, pathogen name (overall relative frequency change, *P* value).

Our major finding based on the isolation of 35,510 pathogens during a 29-year period at a university hospital is the marked increase in HAI with *S aureus*, which moved from second to first in the relative ranking of health care-associated pathogens. Overall, the 3 most common gram-positive pathogens (*S aureus*, CoNS, and *Enterococcus* species) accounted for 34.3% of HAI and the 4 most common gram-negative pathogens (*E coli*, *P aeruginosa*, *Klebsiella* species, and *Enterobacter* species) accounted for 31.0% during the study period from 1980 to 2008. These relative proportions are very similar with a published report from 1990 to 1996, 34% vs 32%, respectively.[3] Comparing the first time block (1980 to 1984) to the last time block (2004 to 2008) showed that these 3 common gram-positive cocci increased by 8.6% (26.8% to 35.4%, respectively), whereas these 4 gram-negative bacilli decreased correspondingly by 6.6% (36.6% to 30.0%, respectively).

The overall increasing relative frequency of *S aureus* that we observed may be explained by an increasingly aging population worldwide and the increasing prevalence of other risk factors for *S aureus* such as diabetes. Noskin et al observed significantly increasing *S aureus* rates per 1,000 patient-days using the Nationwide Inpatient Sample from 1998 to 2003.[9] In addition, MRSA and community-acquired *S aureus* have been documented to contribute to increasing prevalence of *S aureus*.[9,10] Crum et al in a military population demonstrated an increased incidence of both health care-associated and community-associated MRSA.[10] Overall, we demonstrated an increased relative proportion of *S aureus* infections over our 29-year study period despite a relatively constant proportion of *S aureus* that were classified as MRSA for the last 13-year period after adopting a separate code for MRSA. However, *S aureus* relative proportions decreased in recent time blocks, likely because of improved detection (eg, increased laboratory testing) with prompt initiation of isolation precautions and control (eg, improved hand hygiene).

A recent report demonstrated that *C difficile* was a more common health care-associated pathogen than MRSA from 2008 to mid-2009 within a network of 30 community small hospitals in the same geographic area as our institution.[11] Although our analysis showed that the relative frequency of *C difficile* did not surpass the

Table 2
Overall significant percent change of relative frequency of the top 10 pathogens by each site: BSI, UTI, RTI, and SSI

Rank	Pathogen	%			
		BSI	UTI	RTI	SSI
1	*Staphylococcus aureus*	NS	1.4	15.9	20.0
2	*Escherichia coli*	−7.1	−5.6	−3.6	NS
3	Coagulase negative staphylococcus	19.5	NS	NS	NS
4	*Candida* and other yeasts	−3.1	NS	NS	3.0
5	*Enterococcus* spp	10.1	5.7	NS	NS
6	*Pseudomonas aeruginosa*	−3.6	−3.5	NS	−3.3
7	*Klebsiella* spp	−3.1	NS	−4.4	−2.9
8	*Enterobacter* spp	−4.3	NS	−3.7	−2.9
9	Other streptococci	NS	NS	−3.5	NS
10	*Clostridium difficile* and other anaerobes	−3.2	NS	NS	−2.8

BSI, bloodstream infection; *NS*, nonsignificant (significance level: $P < .003$); *RTI*, respiratory tract infection; *SSI*, surgical site infection; *UTI*, urinary tract infection.

relative frequency of *S aureus*, we did observe a 4.0% increase from 1995 to 2008, whereas *S aureus* had a relative frequency decrease of 2.7% in the same time period. This increase in *C difficile* infection has been reported across the United States.[12]

In general, the relative frequency of health care-associated pathogens might be influenced by factors such as the natural viability of microorganisms in the environment as well as the availability and frequency of antimicrobial use.[13] Our findings may be explained by several key factors that may impact the relative frequency of pathogens including the frequent and increased use of broad-spectrum antibiotics, increased use of invasive medical devices, increased immunocompromised patients, and increased antibiotic resistance (eg, MRSA).

The increase of CoNS in BSI may be attributed to the increasing use of broad-spectrum antimicrobials, more immunocompromised patients, increased use of central venous catheters, or the growing recognition of CoNS as a true nosocomial pathogen.[14] However, the decreasing proportion of CoNS among all HAI seen in the last time block (Table 1) may be attributed to overall reductions in BSI rates as a result of multiple interventions[15] as well as the introduction of antibiotics with activity against methicillin-resistant strains such as linezolid, tigecycline, and daptomycin. In addition, because this hospital consistently followed NNIS/NHSN definition changes, generally these relative frequency changes in the 29-year study period may be affected by the changes in the definitions themselves, for example, specifically changes in BSI criteria (eg, CoNS from 2 or more blood cultures). However, we do not believe that this would have a significant impact on the overall long-term trends.

Our study has several limitations. The nature of relative frequency calculation allows a pathogen proportion to change in response to the proportion changes of the other pathogens (ie, when 1 pathogen group increases, another must decrease). In addition, relative frequency calculations are influenced by the magnitude of the actual numbers of pathogens (ie, when overall HAI decrease over time minor changes in absolute pathogen counts can appear more dramatic). Whereas the relative frequencies are useful in describing the epidemiology of HAI pathogens, relative frequencies should be carefully interpreted for these reasons. Thus, a future study with HAI incidence is needed to better interpret these relative frequencies.

This relative frequency of pathogens we estimated here may not be representative of all US hospitals. We were unable to stratify our results by time block, pathogen, and infection site into additional categories of interest, such as intensive care versus nonintensive care patients because of low frequencies. In addition, we could not examine the device-associated specific infection rates because we were unable to obtain device-based denominator information for the entire study period (eg, central line-days) and because we chose to include all infections by infection site regardless of device utilization. Although there have been some changes in diagnostic testing over time, which may make pathogens more easily identified in the laboratory, these changes are unlikely to have a dramatic effect on these results.

Finally, although these relative frequencies showed changes in health care-associated pathogens, detailed changes in the antimicrobial susceptibility data such as extended-spectrum β-lactamase producing pathogens could not be analyzed during the study period because coding for this resistance was not available in the early period and changed over 29 years. To understand the shifts in antimicrobial susceptibility for health care-associated pathogens in the major infection sites over time, further study is needed.

Multiple factors have likely impacted the relative frequency of health care-associated pathogens over time, and, although these factors cannot be controlled for and may not all be defined, these analyses clearly show that the pathogens' proportions have changed over time.

Our data demonstrated the following significant increases in the relative proportion of pathogens during almost 3 decades: *S aureus*, CoNS, *Enterococcus* species, and *C difficile* and other anaerobes. We demonstrated the following significant decreases in pathogens: *E coli*, *P aeruginosa*, *Klebsiella* species, *Enterobacter* species, and other streptococci. By infection site, our results showed significantly increasing trends of *S aureus* in UTI, RTI, and SSI; CoNS in BSI; *Candida* in SSI; and *Enterococcus* in BSI and UTI.

Given the lack of development of new antibiotics and growing importance of changes in health care-associated pathogens including antimicrobial resistance, it is crucial to assess and explore factors which lead to changes in pathogen frequencies so that infection control strategies can be modified to reflect these changes.

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