Infection *versus* cardiovascular disease as leading causes of hospitalisations and associated mortality in vasculitis in the U.S.: a national study

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ABSTRACT

Objective. *To assess the top 5 causes of non-vasculitis hospitalisations in people with vasculitis over time.*

Methods. *In a national U.S. sample of people with vasculitis hospitalised for reasons other than vasculitis, the rank (and percent) of top 5 causes of hospitalisations and in-hospital mortality were compared in 1998-99 versus 2013-2014.*

Results. *The top 5 ranked disease categories responsible for non-vasculitis hospitalisations in people with vasculitis in 1998-99 versus 2013-14 were as follows, respectively: (#1) circulatory system disease versus the same; (#2) heart disease versus infections/parasitic diseases; (#3) digestive system disease versus bacterial infection; (#4) respiratory disease versus septicaemia; and (#5) musculoskeletal disease versus unspecified septicaemia. The respective top 5 CCS category ranks for in-hospital mortality in people with vasculitis in 1998-1999 versus 2013-2014 were: (#1) respiratory disease versus infections/parasitic diseases; (#2) circulatory system disease versus bacterial infection; (#3) heart disease versus septicaemia; (#4) respiratory infection versus unspecified septicaemia; and (#5) pneumonia versus circulatory system disease.*

Conclusions. *Infections replaced cardio-pulmonary disease among the top 5 causes for non-primary vasculitis hospitalisations and associated in-hospital mortality in people with vasculitis over time. Studies should examine modifiable factors associated with infection in vasculitis and design interventions to reduce this burden.*

Introduction

Vasculitis is a systemic disease with high morbidity and mortality, related to both disease and treatment-related complications (1). A systematic review concluded that renal failure, active disease and infection were the main causes of mortality in vasculitis (2); mortality was higher in Takayasu's disease (TAK) compared to the general population (3). A two-centre UK-based study of 100 people with AAV found that 28% were hospitalised for infection in 2004-2011 (4). A 1997-2011 single-centre Chinese study of 398 people with ANCA-associated vasculitis (AAV) with 83 deaths reported infection and cardiovascular disease as leading causes of early *versus* late (>12 months after diagnosis) deaths (5). In a more recent 2015-2018 single U.S. tertiary-care centre study of 54 patients with AAV, 2/3rd of hospitalisations were for non-vasculitis reasons (6). Infection was the most common reason for hospitalisation (41%) and responsible for all four in-hospital deaths (6). These observations raised the question whether the causes of hospitalisation and mortality in vasculitis have changed over time.

Limitations of previous studies were that most were single centres, had small sample sizes (<400) and were limited to AAV. A different time-period and country setting did not allow comparison of in-hospital morbidity/mortality burden across time. Therefore, an epidemiological study is needed to fill this knowledge gap. This study examined the hypothesis whether infection has replaced cardiovascular disease among the top 5 causes of non-vasculitis hospitalisations in people with vasculitis in the U.S. over time.

Methods

This study used the 1998-2014 U.S. Nationwide Inpatient Sample (NIS), a component of the healthcare cost, and utilisation project (HCUP) (7). The

NIS is a de-identified national all-payer inpatient health care database that represents all U.S. hospital discharges, since it is a 20% stratified random sample of all U.S. hospitalisations. The Institutional Review Board at the University of Alabama at Birmingham (UAB; X120207004) approved this study.

People with vasculitis as a secondary diagnosis were identified based on the presence of ICD-9-CM code of 446.xx, an approach with a sensitivity of 94% and specificity of 95% (8). We examined patient characteristics in 1998-1999 (the first period) and 2013-2014 (the last period). The rank frequency of the top 25 Clinical Classification Software (CCS) [a standardised system for clustering diagnoses and procedures (primary or secondary) was developed using manageable clinically meaningful groups (9)] categories for all patients hospitalised with non-primary vasculitis diagnosis. The study assessed whether ranking of cardiovascular *versus* infection CCS categories changed between 1998-1999 (the first period) and 2013-2014 (the last period); and compared it to the U.S. general population. This study was limited to 2014, since ICD-9-CM switched to ICD-10-CM in 2015 in the U.S.

Table I. Demographic characteristics of non-vasculitis hospitalisations in people with vasculitis, comparing 1998-1999 to 2013-2014.

	First period 1998-1999 (n=65,683)	Last period 2013-2014 (n=82,348)
Age, Mean (SE); Median	68.1 (0.16); 73.4	64.9 (0.15); 68.8
Age category		
<50	10,465 (15.9%)	15,858 (19.3%)
50-64	9,080 (13.8%)	17,311 (21.0%)
65-79	26,354 (40.1%)	27,263 (33.1%)
≥80	19,784 (30.1%)	21,912 (26.6%)
Sex		
Male	20,710 (31.5%)	29,897 (36.3%)
Female	44,969 (68.5%)	52,440 (63.7%)
Race		
White	43,907 (66.8%)	58,419 (70.9%)
Black	4,661 (7.1%)	8,921 (10.8%)
Hispanic	2,173 (3.3%)	6,020 (7.3%)
Other/Missing	14,942 (22.7%)	8,988 (10.9%)
Deyo-Charlson Score		
0	21,377 (32.5%)	3,784 (4.6%)
1	19,804 (30.2%)	7,578 (9.2%)
≥2	24,503 (37.3%)	70,986 (86.2%)
Vasculitis type		
Polyarteritis nodosa	4,436 (6.8%)	7,853 (9.5%)
Wegener's granulomatosis	10,154 (15.5%)	21,603 (26.2%)
Giant cell arteritis	34,993 (53.3%)	31,317 (38.0%)
Takayasu's disease	1,113 (1.7%)	2,312 (2.8%)
Other	4,712 (7.2%)	8,446 (10.2%)

Results

Patient characteristics for non-primary vasculitis hospitalisation in people with vasculitis

The mean (median) age of non-primary vasculitis hospitalisation in people with vasculitis was 68 (73) years in 1998–1999 *versus* 65 (69) years in 2013-14 (Table I). Of these, 36% were male, and 71% were white in 2013-14, with minimal/no changes compared to 1998-1999. Medical comorbidity increased over time with a larger proportion with Deyo-Charlson comorbidity index of 2 or more in 2013-14 *versus* 1998–1999. Giant cell arteritis decreased while polyarteritis nodosa and Wegener's granulomatosis diagnosis increased in vasculitis hospitalisations over time (Table I).

Top CCS categories for non-primary vasculitis hospitalisation in people with vasculitis, and time-trends

In 1998-1999 *versus* 2013-2014, there were 69,170 *versus* 86,720 non-primary vasculitis hospitalisations. The top 5 CCS categories associated with non-primary vasculitis hospitalisations in 1998-99 were circulatory system disease, heart disease, digestive system disease, respiratory disease, and musculoskeletal disease (Ranks 1-5 in order, respectively; Fig. 1). In 2013–2014, the top 5 CCS categories were circulatory system disease (rank #1→1), infections/parasitic diseases (rank #10→2), bacterial infection (rank #11→3), septicaemia (rank #12→4), and unspecified septicaemia (rank #18→4; Fig. 1). Compared to 27.7% non-primary vasculitis hospitalisations associated with circulatory system disease in 1998-99, 21.3% were associated in 2013-2014.

Comparatively, in 2013-2014, the top 5 CCS categories for hospitalisations in the general U.S. population were as follows (rank in 1998-1999 → rank in 2013-2014): circulatory system disease (rank #1→1), complications of pregnancy; childbirth; and the puerperium (rank #3→2), certain conditions originating in the perinatal period (rank #4→3), liveborn (rank #5→4), and diseases of the heart (rank #3→2; Fig. 2).

Top CCS categories for in-hospital deaths in people with vasculitis, and time-trends

In 1998-1999 *versus* 2013-2014, there were 817 *versus* 766 deaths during non-primary vasculitis hospitalisations. The top 5 CCS categories associated with in-hospital death for non-primary vasculitis hospitalisations in 1998–1999 were respiratory disease, circulatory system disease, heart disease, respiratory infection and pneumonia (Ranks 1-5 in order, respectively; Fig. 3). In 2013–2014, these were infections/parasitic diseases (rank #6→1), bacterial infection (rank #7→2), septicaemia (rank #9→3), unspecified septicaemia (rank #22→4), and circulatory system disease (rank #1→5; Fig. 3). In 1998-99, the top 3 CCS categories were all cardio-pulmonary diseases; in 2013-14, the top three CCS categories were all infections (Fig. 3). Compared to 26.4% non-primary vasculitis hospitalisation deaths associated with circulatory system disease in 1998-1999, 20.5% were associated in 2013-2014.

Comparatively, in 2013-2014, the top 5 CCS categories for in-hospital mortality in the general U.S. population were as fol-

Hospitalization claims, 1998-1999 (69,170 non-primary vasc claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the circulatory system (7)	461,745 (27.7)	1
Diseases of the heart (7.2)	321,175 (19.3)	2
Diseases of the digestive system (9)	177,205 (10.6)	3
Diseases of the respiratory system (8)	155,240 (9.3)	4
Diseases of the musculoskeletal system and connective tissue (13)	143,095 (8.6)	5
Injury and poisoning (16)	141,265 (8.5)	6
Congestive heart failure; nonhypertensive [108.] (7.2.11)	128,570 (7.7)	7
Diseases of the genitourinary system (10)	127,820 (7.7)	8
Diseases of the urinary system (10.1)	120,750 (7.3)	9
Infectious and parasitic diseases (1)	104,720 (6.3)	10
Bacterial infection (1.1)	98,145 (5.9)	11
Septicemia (except in labor) [2.] (1.1.2)	97,475 (5.9)	12
Non-traumatic joint disorders (13.2)	84,505 (5.1)	13
Osteoarthritis [203.] (13.2.2)	79,125 (4.8)	14
Complications (16.10)	76,340 (4.6)	15
Acute and unspecified renal failure [157.] (10.1.2)	74,635 (4.5)	16
Acute renal failure (10.1.2.1)	74,605 (4.5)	17
Unspecified septicemia (1.1.2.6)	71,700 (4.3)	18
Endocrine; nutritional; and metabolic diseases and immunity (3)	70,735 (4.2)	19
Osteoarthritis; localized (13.2.2.1)	68,040 (4.1)	20
Respiratory infections (8.1)	65,595 (3.9)	21
Neoplasms (2)	65,065 (3.9)	22
Symptoms; signs; and ill-defined conditions and factors	62,060 (3.7)	23
Cerebrovascular disease (7.3)	58,850 (3.5)	24
Cardiac dysrhythmias [106.] (7.2.9)	58,500 (3.5)	25

Hospitalization claims, 2013-2014 (86,720 non-primary vasc claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the circulatory system (7)	2,315 (21.3)	1
Infectious and parasitic diseases (1)	2,300 (21.2)	2
Bacterial infection (1.1)	2,125 (19.6)	3
Septicemia (except in labor) [2.] (1.1.2)	2,105 (19.4)	4
Unspecified septicemia (1.1.2.6)	1,420 (13.1)	5
Diseases of the heart (7.2)	1,415 (13.0)	6
Diseases of the respiratory system (8)	1,270 (11.7)	7
Injury and poisoning (16)	1,025 (9.4)	8
Diseases of the digestive system (9)	865 (8.0)	9
Diseases of the genitourinary system (10)	715 (6.6)	10
Diseases of the urinary system (10.1)	690 (6.4)	11
Complications (16.10)	635 (5.8)	12
Congestive heart failure; nonhypertensive [108.] (7.2.11)	530 (4.9)	13
Respiratory infections (8.1)	490 (4.5)	14
Complication of device; implant or graft [237.] (16.10.1)	485 (4.5)	15
Symptoms; signs; and ill-defined conditions and factors infl (17)	470 (4.3)	16
Acute and unspecified renal failure [157.] (10.1.2)	460 (4.2)	17
Acute renal failure (10.1.2.1)	460 (4.2)	18
Endocrine; nutritional; and metabolic diseases and immunity (3)	450 (4.1)	19
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	440 (4.1)	20
Respiratory failure; insufficiency; arrest (adult)	380 (3.5)	21
Respiratory failure (8.6.1)	375 (3.5)	22
Neoplasms (2)	335 (3.1)	23
Diseases of the musculoskeletal system and connective tissue (13)	335 (3.1)	24
Pneumonia; organism unspecified (8.1.1.3)	320 (2.9)	25

Fig. 1. Top 25 healthcare cost and utilisation project (HCUP) Clinical Classifications Software (CCS) categories for non-vasculitis hospitalisations in people with vasculitis, comparing 1998-1999 to 2013-2014, with respective ranks.
The figure shows the top 25 CCS categories for hospitalisation for the first period, 1998-1999 (left) and the last study period, 2013-2014 (right). Each CCS category label and category are shown in the first column, followed by the number and percent of discharges of all hospitalisations in the next column, followed by the relative rank from 1-25. Square brackets show the single-level CCS categories and regular brackets show multi-level CCS categories. Red arrows indicate any category that went to a higher rank in 2013-2014 and green indicates those any category that descended to a lower rank in 2013-2014. Solid black arrows show the categories whose rank remained the same. Number of discharges (percent) for each CCS category and rank is shown next to each CCS category. CCS categories included diagnoses in primary or non-primary position with vasculitis in non-primary position for hospitalisations in people with vasculitis. CCS consists of two related classification systems, single-level and multi-level. Single-level CCS system classifies all diagnoses and procedures. The single-level *diagnosis CCS* aggregates illnesses and conditions into 285 mutually exclusive categories. Most of these categories are homogeneous; for example, CCS category #100 is "Acute myocardial infarction and #101 is "Coronary atherosclerosis and other heart disease". Some CCS categories combine several less common, individual conditions, such as CCS category #3, which is "Other Bacterial Infections. Similarly, the single-level procedure CCS aggregates procedures into 231 mutually exclusive categories, most representing single types of procedures. For example, #43 is "Heart valve procedures", #44 is "Coronary artery bypass graft (CABG)" and #45 is "Percutaneous transluminal coronary angioplasty (PTCA)".
The multi-level CCS expands the single-level CCS into a hierarchical system. The multi-level CCS groups single-level CCS categories into broader body systems or condition categories. It also splits single-level CCS categories to provide more detail. The multi-level system has four levels for diagnoses and three levels for procedures, which provide the opportunity to examine general groupings or to assess very specific conditions and procedures.

lows (rank in 1998-1999→ rank in 2013-2014): infectious and parasitic diseases (rank #7→1), bacterial infection (rank #11→2), septicaemia (except in labour) (rank #12→3), diseases of the circulatory system (rank #1→4), and unspecified septicaemia (rank #21→5; Fig. 4).

Discussion

Using the national U.S. NIS data, top causes of non-primary vasculitis hospitalisations and associated in-hospital mortality were compared across 17-years. Even though circulatory system diseases were rank #1 in both periods for non-vasculitis hospitalisations in vasculitis, the proportion of associated hospitalisations decreased from 27.7% in 1998-99 to 21.3% in 2013-2014. Infections replaced cardio-respiratory disease in 4 of the 5 top causes of death from 1998-1999 to 2013-2014. These 5 top CCS categories for hospitalisations in vasculitis differed from the U.S. general population in both first and the last study periods. In 2013-2014, except for circulatory system diseases (ranked #1 in both periods as well), the 5 top CCS categories for hospitalisations in the U.S. general population differed from vasculitis: pregnancy and child-birth were ranks #2, #3 and #4, and heart disease ranked #5.

Consistent with this study hypothesis, infections replaced 4 of the top 5 ranks of non-primary vasculitis hos-

Hospitalization claims, 1998-1999 (68,364,626 NIS claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the circulatory system (7)	12,597,783 (18.4)	1
Diseases of the heart (7.2)	8,933,315 (13.1)	2
Complications of pregnancy; childbirth; and the puerperium (11)	8,320,461 (12.2)	3
Certain conditions originating in the perinatal period (15)	7,629,636 (11.2)	4
Liveborn [218.] (15.1)	7,396,427 (10.8)	5
Diseases of the respiratory system (8)	6,670,065 (9.8)	6
Diseases of the digestive system (9)	5,860,657 (8.6)	7
Injury and poisoning (16)	5,112,156 (7.5)	8
Neoplasms (2)	3,800,653 (5.6)	9
Mental illness (5)	3,705,155 (5.4)	10
Respiratory infections (8.1)	3,325,481 (4.9)	11
Diseases of the genitourinary system (10)	3,068,223 (4.5)	12
Diseases of the musculoskeletal system and connective tissue (13)	2,744,208 (4.0)	13
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	2,595,172 (3.8)	14
Coronary atherosclerosis and other heart disease [101.] (7.2.4)	2,487,917 (3.6)	15
Endocrine; nutritional; and metabolic diseases and immunity (3)	2,168,782 (3.2)	16
Symptoms; signs; and ill-defined conditions and factors infl (17)	2,132,906 (3.1)	17
Indications for care in pregnancy; labor; and delivery (11.4)	2,094,508 (3.1)	18
Coronary atherosclerosis (7.2.4.4)	2,094,382 (3.1)	19
Complications during labor (11.5)	2,078,537 (3.0)	20
Complications mainly related to pregnancy (11.3)	2,061,603 (3.0)	21
Pneumonia; organism unspecified (8.1.1.3)	1,953,423 (2.9)	22
Congestive heart failure; nonhypertensive [108.] (7.2.11)	1,943,352 (2.8)	23
Cerebrovascular disease (7.3)	1,929,469 (2.8)	24
Congestive heart failure (7.2.11.1)	1,882,670 (2.8)	25

Hospitalization claims, 2013-2014 (70,956,610 NIS claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the circulatory system (7)	10,312,215 (14.5)	1
Complications of pregnancy; childbirth; and the puerperium (11)	8,191,693 (11.5)	2
Certain conditions originating in the perinatal period (15)	7,844,028 (11.1)	3
Liveborn [218.] (15.1)	7,579,498 (10.7)	4
Diseases of the heart (7.2)	6,824,155 (9.6)	5
Diseases of the digestive system (9)	6,576,409 (9.3)	6
Diseases of the respiratory system (8)	6,029,708 (8.5)	7
Injury and poisoning (16)	5,603,270 (7.9)	8
Diseases of the musculoskeletal system and connective tissue (13)	4,166,087 (5.9)	9
Mental illness (5)	4,116,100 (5.8)	10
Infectious and parasitic diseases (1)	3,222,130 (4.5)	11
Diseases of the genitourinary system (10)	3,149,529 (4.4)	12
Neoplasms (2)	2,988,645 (4.2)	13
Complications mainly related to pregnancy (11.3)	2,866,249 (4.0)	14
Bacterial infection (1.1)	2,843,525 (4.0)	15
Septicemia (except in labor) [2.] (1.1.2)	2,811,130 (4.0)	16
Endocrine; nutritional; and metabolic diseases and immunity (3)	2,576,850 (3.6)	17
Diseases of the urinary system (10.1)	2,565,395 (3.6)	18
Respiratory infections (8.1)	2,467,429 (3.5)	19
Non-traumatic joint disorders (13.2)	2,200,826 (3.1)	20
Complications (16.10)	2,189,705 (3.1)	21
Unspecified septicemia (1.1.2.6)	2,127,200 (3.0)	22
Indications for care in pregnancy; labor; and delivery (11.4)	2,104,199 (3.0)	23
Osteoarthritis [203.] (13.2.2)	2,093,531 (3.0)	24
Lower gastrointestinal disorders (9.6)	2,037,980 (2.9)	25

Fig. 2. Top 25 healthcare cost and utilisation project (HCUP) Clinical Classifications Software (CCS) categories for hospitalisations in the U.S. general population, comparing 1998-1999 to 2013-2014, with respective ranks.
For the legend please refer to Fig. 1.

pitalisations in 2013-2014, rank #2-#4 each responsible for 19-21% of these hospitalisations and rank #5 for 13%. The relative contribution of infections to non-primary vasculitis hospitalisations increased over time, while that of cardiovascular disease decreased. This may be partially due to a higher awareness of increased cardiovascular disease risk in people with vasculitis (10) which may lead to higher rates of early detection and better management; more outpatient rather than inpatient treatment of cardiac conditions over time (11); a reduction of cardiovascular disease due to more effective suppression of systemic and vascular inflammation including C-reactive protein with treatments including biologics (12); and/or increasing use of immunosuppressives, biologics and glucocorticoids (13, 14) that increase the risk of infections (15). The study finding of increasing medical comorbidity over time can also partially explain increasing infection causes for hospitalisation. Whether a change in vasculitis subtypes over time impacted the top CCS categories cannot be assessed in this study in the absence of disease activity, organ involvement, and medication use.

In contrast, in the general U.S. population, infectious causes ranked #11, 15, 16, 19 and 22 for hospitalisations in 2013–2014, each accounting for 3–4% of all hospitalisations, *i.e.* much lower ranks and proportions compared to that in vasculitis in 2013-2014. This finding supports the excess infection risk in vasculitis hospitalisations compared to the general U.S. population.

In 1998-1999, the top 3 CCS categories associated with in-hospital mortality were all cardio-pulmonary diseases. In contrast in 2013-2014, the top three CCS categories for non-vasculitis hospitalisations in vasculitis were all infections, similar to U.S. general population. These findings extend single centre study findings of the infection as the most common cause of in-hospital mortality in vasculitis to the U.S. national sample (5, 6). The increasing importance of infection in people with vasculitis over time is evident.

These study findings must be interpreted considering study limitations. Misclassification bias due to the use of diagnostic codes is possible. The lack of medication and laboratory data in NIS limits these important analyses. A more frequent use of immunosuppressives, biologics and glucocorticoids over time could have contributed to increased infection-related hospitalisations and mortality in vasculitis. Analyses by vasculitis sub-types is beyond the scope of this study; future studies should examine these questions. The study strengths include the use of a national database, a large sample size, and standardised CCS categories.

Died in-hospital First Period, 1998-1999 (817 non-primary vasc claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the respiratory system (8)	223 (27.3)	1
Diseases of the circulatory system (7)	216 (26.4)	2
Diseases of the heart (7.2)	115 (14.1)	3
Respiratory infections (8.1)	115 (14.1)	4
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	113 (13.8)	5
Infectious and parasitic diseases (1)	85 (10.4)	6
Bacterial infection (1.1)	68 (8.3)	7
Pneumonia; organism unspecified (8.1.1.3)	68 (8.3)	8
Septicemia (except in labor) [2.] (1.1.2)	66 (8.1)	9
Diseases of the digestive system (8)	65 (7.9)	10
Neoplasms (2)	52 (6.4)	11
Cerebrovascular disease (7.3)	52 (6.4)	12
Respiratory failure; insufficiency; arrest (adult) [131.] (8.6)	50 (6.1)	13
Acute cerebrovascular disease [109.] (7.3.1)	50 (6.1)	14
Respiratory failure (8.6.1)	48 (5.9)	15
Acute myocardial infarction [100.] (7.2.3)	41 (5)	16
Diseases of the genitourinary system (10)	38 (4.6)	17
Diseases of the urinary system (10.1)	37 (4.5)	18
Congestive heart failure; nonhypertensive [108.] (7.2.11)	37 (4.5)	19
Congestive heart failure	37 (4.5)	20
Diseases of arteries; arterioles; and capillaries (7.4)	36 (4.4)	21
Unspecified septicemia (11.2.6)	36 (4.4)	22
Injury and poisoning (16)	35 (4.3)	23
Acute and unspecified renal failure [157.] (10.1.2)	32 (3.9)	24
Acute renal failure (10.1.2.1)	32 (3.9)	25

Died in-hospital Last Period, 2013-2014 (766 non-primary vasc claims)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Infectious and parasitic diseases (1)	252 (32.9)	1
Bacterial infection (1.1)	231 (30.2)	2
Septicemia (except in labor) [2.] (1.1.2)	229 (29.9)	3
Unspecified septicemia (1.1.2.6)	165 (21.6)	4
Diseases of the circulatory system (7)	157 (20.5)	5
Diseases of the respiratory system (8)	129 (16.9)	6
Diseases of the heart (7.2)	85 (11.1)	7
Respiratory failure; insufficiency; arrest (adult) [131.] (8.6)	58 (7.6)	8
Respiratory failure (8.6.1)	58 (7.6)	9
Diseases of the digestive system (9)	48 (6.3)	10
Injury and poisoning (16)	44 (5.8)	11
Cerebrovascular disease (7.3)	43 (5.6)	12
Neoplasms (2)	42 (5.5)	13
Acute cerebrovascular disease [109.] (7.3.1)	41 (5.4)	14
Respiratory infections (8.1)	37 (4.8)	15
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	33 (4.3)	16
Diseases of the genitourinary system (10)	27 (3.5)	17
Diseases of the urinary system (10.1)	27 (3.5)	18
Congestive heart failure; nonhypertensive [108.] (7.2.11)	26 (3.4)	19
Occlusion of cerebral arteries (7.3.1.2)	25 (3.3)	20
Pneumonia; organism unspecified (8.1.1.3)	25 (3.3)	21
Acute myocardial infarction [100.] (7.2.3)	24 (3.1)	22
Complications (16.1)	22 (2.9)	23
Acute and unspecified renal failure [157.] (10.1.2)	20 (2.6)	24
Other gram negative septicemia (1.1.2.4)	20 (2.6)	25

Fig. 3. Top 25 healthcare cost and utilisation project (HCUP) Clinical Classifications Software (CCS) categories for In-hospital death for non-vasculitis hospitalisations in people with vasculitis, comparing 1998-1999 to 2013-2014.
The figure shows the top 25 CCS categories for In-hospital death for hospitalisations for the first period, 1998-1999 (left) and the last study period, 2013-2014 (right). Each CCS category label and category are shown in the first column, followed by the number and percent of discharges of all hospitalisations in the next column, followed by the relative rank from 1-25. Square brackets show the single-level CCS categories and regular brackets show multi-level CCS categories. Red arrows indicate any category that went to a higher rank in 2013-2014 and green indicates those any category that descended to a lower rank in 2013-2014. Solid black arrows show the categories whose rank remained the same. Number of discharges (percent) for each CCS category and rank is shown next to each CCS category.

Conclusion

In conclusion, the epidemiology of in-hospital morbidity/mortality is changing in vasculitis. Infection is increasingly responsible for non-primary vasculitis hospitalisations and associated in-hospital mortality in people with vasculitis from 1998-1999 to 2013-2014, *versu*s cardiovascular disease. Future studies should examine modifiable factors associated with infections in vasculitis. A better understanding of the infection risk can help in designing interventions to reduce its incidence, and potentially reduce infection-associated morbidity and mortality in vasculitis.

Take home messages

- Infections accounted for four of top five hospitalisation causes of non-vasculitis hospitalisations in people with vasculitis in 2013–2014.
- Infections replaced cardio-respiratory disease in 4 of the 5 top causes of death in hospitalised vasculitis patients from 1998-1999 to 2013-2014.
- Infection were far more common causes of hospitalisations in people with vasculitis in 2013-14 compared to the U.S. general population.

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Availability of data and materials

These data are easily available from the Agency for Healthcare Research and Quality (AHRQ's) "Healthcare Cost and Utilization Project (HCUP)" and can be obtained after completing an on-line Data Use Agreement training session and signing a Data Use Agreement. (e-mail: HCUPDistributor@ahrq.gov).

Competing interests

J.A. Singh has received consultant fees from Crealta/Horizon, Medisys, Fidia, UBM LLC, Trio health, Medscape, WebMD, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, Practice Point communications, the National Institutes of Health and the American College of Rheumatology. He owns stock options in Vaxart Pharmaceuticals and Charlottes' Web Holdings Inc.

Died in-hospital First Period, 1998-1999 (1,698,105 deaths)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Diseases of the circulatory system (7)	505,380 (29.8)	1
Diseases of the respiratory system (8)	369,390 (21.8)	2
Diseases of the heart (7.2)	303,380 (17.9)	3
Neoplasms (2)	231,315 (13.6)	4
Respiratory infections (8.1)	152,881 (9.0)	5
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	150,762 (8.9)	6
Infectious and parasitic diseases (1)	136,583 (8.0)	7
Cerebrovascular disease (7.3)	135,452 (8.0)	8
Acute cerebrovascular disease [109.] (7.3.1)	131,539 (7.7)	9
Acute myocardial infarction [100.] (7.2.3)	124,717 (7.3)	10
Bacterial infection (1.1)	115,018 (6.8)	11
Septicemia (except in labor) [2.] (1.1.2)	113,082 (6.7)	12
Diseases of the digestive system (9)	112,618 (6.6)	13
Injury and poisoning (16)	106,721 (6.3)	14
Pneumonia; organism unspecified (8.1.1.3)	102,407 (6.0)	15
Congestive heart failure; nonhypertensive [108.] (7.2.11)	92,896 (5.5)	16
Respiratory failure; insufficiency; arrest (adult) [131.] (8.6)	91,467 (5.4)	17
Congestive heart failure (7.2.11.1)	89,363 (5.3)	18
Respiratory failure (8.6.1)	85,831 (5.1)	19
Aspiration pneumonitis; food/vomitus [129.] (8.4)	69,021 (4.1)	20
Unspecified septicemia (1.1.2.6)	66,568 (3.9)	21
Intracranial hemorrhage (7.3.1.1)	64,073 (3.8)	22
Secondary malignancies [42.] (2.12)	63,074 (3.7)	23
Occlusion of cerebral arteries (7.3.1.2)	49,590 (2.9)	24
Cancer of bronchus; lung [19.] (2.3)	48,129 (2.8)	25

Died in-hospital Last Period, 2013-2014 (1,344,310 deaths)		
CCS Label (CCS Category)	Discharges N(%)	Rank
Infectious and parasitic diseases (1)	342,450 (25.5)	1
Bacterial infection (1.1)	330,800 (24.6)	2
Septicemia (except in labor) [2.] (1.1.2)	330,150 (24.6)	3
Diseases of the circulatory system (7)	313,805 (23.3)	4
Unspecified septicemia (1.1.2.6)	269,830 (20.1)	5
Diseases of the respiratory system (8)	217,475 (16.2)	6
Diseases of the heart (7.2)	184,340 (13.7)	7
Neoplasms (2)	111,610 (8.3)	8
Injury and poisoning (16)	108,215 (8.0)	9
Respiratory failure; insufficiency; arrest (adult) [131.] (8.6)	100,985 (7.5)	10
Respiratory failure (8.6.1)	97,745 (7.3)	11
Cerebrovascular disease (7.3)	93,850 (7.0)	12
Acute cerebrovascular disease [109.] (7.3.1)	91,505 (6.8)	13
Diseases of the digestive system (9)	81,885 (6.1)	14
Acute myocardial infarction [100.] (7.2.3)	60,240 (4.5)	15
Respiratory infections (8.1)	57,085 (4.2)	16
Pneumonia (except that caused by TB or STD) [122.] (8.1.1)	54,035 (4.0)	17
Congestive heart failure; nonhypertensive [108.] (7.2.11)	52,960 (3.9)	18
Intracranial hemorrhage (7.3.1.1)	49,610 (3.7)	19
Pneumonia; organism unspecified (8.1.1.3)	43,930 (3.3)	20
Occlusion of cerebral arteries (7.3.1.2)	41,745 (3.1)	21
Diseases of the genitourinary system (10)	40,350 (3.0)	22
Diseases of the urinary system (10.1)	39,615 (2.9)	23
Intracranial injury [233.] (16.4)	33,785 (2.5)	24
Other intracranial injury (16.4.2)	33,515 (2.5)	25

Fig. 4. Top 25 healthcare cost and utilisation project (HCUP) Clinical Classifications Software (CCS) categories for In-hospital death for hospitalisations in the U.S. general population, comparing 1998-1999 to 2013-2014. For the legend please refer to Fig. 3.

He has previously owned stock options in Amarin, Viking and Moderna Phamaceuticals. He is on the speaker's bureau of Simply Speaking and is a member of the executive of OMERACT, an organisation that develops outcome measures in rheumatology and receives arms-length funding from 12 companies. He serves on the FDA Arthritis Advisory Committee and is the chair of the Veterans Affairs Rheumatology Field Advisory Committee. He is the editor and the Director of the University of Alabama at Birmingham Cochrane Musculoskeletal Group Satellite Center on Network Meta-analysis.

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