

## Etiology of Above-knee Amputations in the United States: Is Periprosthetic Joint Infection an Emerging Cause?

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### Abstract

**Background** Above-knee amputation (AKA) is a morbid procedure and is performed for a number of conditions. Although AKA is usually performed for dysvascular disease, trauma, and malignancy, AKA is also considered in patients who have failed multiple salvage attempts at treating periprosthetic joint infection (PJI) of TKA. Although aggressive measures are being taken to treat PJI, the huge volume of TKAs might result in a large number of AKAs being performed for PJI in the United States. However, the national trends in the incidence of AKAs from different etiologies and the relative contribution of different etiologies to AKA are yet to be studied.

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Each author certifies that his or her institution waived approval for the human protocol for this investigation and that all investigations were conducted in conformity with ethical principles of research. This work was performed at Cleveland Clinic, Cleveland, OH, USA. All ICMJE Conflict of Interest Forms for authors and *Clinical Orthopaedics and Related Research*® editors and board members are on file with the publication and can be viewed on request.

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**Questions/purposes** (1) What are the temporal trends in the incidence of AKAs (from all causes) in the US population from 1998 to 2013? (2) What are the temporal trends in the incidence of AKAs by etiology (dysvascular disease, trauma, malignancy, and PJI)? (3) What are the temporal trends in the relative contribution of different etiologies to AKA?

**Methods** Using the Nationwide Inpatient Sample (NIS) from 1998 to 2013, AKAs were identified using International Classification of Diseases, 9<sup>th</sup> Revision (ICD-9) procedure code 84.17. The NIS database is the largest all-payer database in the United States containing information on approximately 20% of all the hospital admissions in the country. As a result of its sampling design, it allows for estimation of procedural volumes at the national level. All AKAs were grouped into one of the following five etiologies in a sequential manner using ICD-9 diagnosis codes: malignancy, PJI, trauma, dysvascular disease (peripheral vascular disease, diabetic, or a combination), and others. All of the numbers were converted to national estimates using sampling weights provided by the NIS, and the national incidence of AKAs resulting from various etiologies was calculated using the US population as the denominator. Poisson and linear regression analyses were used to analyze the annual trends.

**Results** From 1998 to 2013, the incidence of AKAs decreased by 47% from 174 to 92 AKAs per 1 million adults (incidence rate ratio [IRR]; change in the number of AKAs per 1 million adults per year; 0.96; 95% confidence interval [CI], 0.96-0.96;  $p < 0.001$ ). The incidence of AKAs resulting from PJI increased by 263% (IRR, 1.07; 95% CI, 1.06-1.07;  $p < 0.001$ ). An increase was also observed for AKAs from malignancy (IRR, 1.01; 95% CI, 1.00-1.02;  $p = 0.007$ ), although to a smaller extent. AKAs from dysvascular causes (IRR, 0.96; 95% CI, 0.95-0.96;  $p < 0.001$ ) and other etiologies (IRR, 0.97; 95% CI, 0.96-0.97;  $p < 0.001$ ) decreased. There

was no change in the incidence of AKAs related to trauma (IRR, 1.00; 95% CI, 0.99-1.00;  $p = 0.088$ ). The proportion of AKAs resulting from PJI increased by 589% from 1998 to 2013 (coefficient = 0.18; 95% CI, 0.15-0.22;  $p < 0.001$ ). The proportion of AKAs resulting from dysvascular causes decreased (coefficient = 0.18; 95% CI, 0.15-0.22;  $p < 0.001$ ), whereas that resulting from malignancy (coefficient = 0.04; 95% CI, 0.03-0.05;  $p < 0.001$ ) and trauma (coefficient = 0.13; 95% CI, 0.09-0.18;  $p < 0.001$ ) increased.

**Conclusions** The incidence of AKAs has decreased in the United States. AKAs related to dysvascular disease and other etiologies such as trauma and malignancy have either substantially decreased or remained fairly constant, whereas that resulting from PJI more than tripled. Given the increased resource utilization associated with limb loss, the results of this study suggest that national efforts to reduce disability should prioritize PJI. Further studies are required to evaluate the risk factors for AKA from PJI and to formulate better strategies to manage PJI.

**Level of Evidence** Level III, therapeutic study.

## Introduction

Above-knee amputation (AKA) is a morbid procedure associated with substantial impairment of patients' quality of life [4, 6, 9, 14]. Peripheral vascular disease with or without diabetes, trauma, and malignancy have been historically considered the leading causes of AKA [5, 7, 24, 38, 44]. Periprosthetic joint infection (PJI) is another important cause of AKA. Despite the advancements in TKA and measures to prevent infection, PJI continues to be a challenging complication of TKA [12, 22, 28]. Although the incidence of PJI after primary TKA is as low as 1%, the success of treatment of PJI is only approximately 60% to 80% [3, 28, 34, 37, 40]. The success of treatment of PJI decreases further with each subsequent revision, and AKA is sometimes considered in some patients who have failed multiple salvage attempts at treating PJI [13, 41].

In a study using the Medicare database, Son et al. [42] reported that surgeons are more aggressive in managing PJI because they found a decrease in the risk of AKA after an infected TKA. However, their study did not evaluate the incidence of AKAs from PJI in the US population. It is estimated that > 650,000 TKAs are performed each year in the United States with > 5 million people living with one [1, 32]. With such high volumes of TKAs, the number of AKAs performed for PJI is expected to be large even when the incidence of AKA after TKA is very low. Given the economic, health, and social implications of AKAs, various measures have been successfully implemented to reduce the number of AKAs, especially those from dysvascular disease [18, 20, 39]. Because future measures

to reduce AKAs depend on the etiologies of AKAs, it is important to understand the reasons for AKA in the nation. However, there is limited literature about the national trends in etiologies of AKAs.

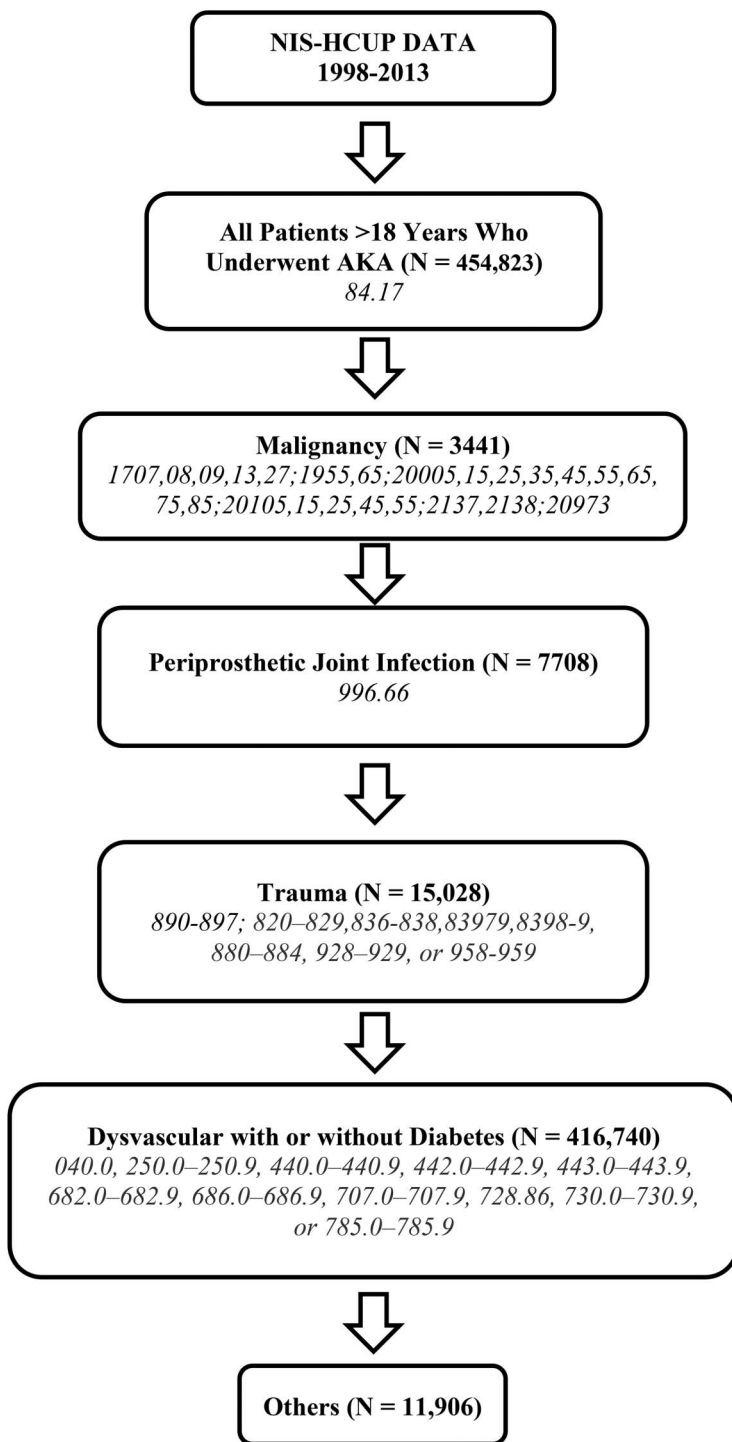
## Study Questions

(1) What are the temporal trends in the incidence of AKAs (from all causes) in the United States from 1998 to 2013? (2) What are the temporal trends in the incidence of AKAs by etiology (dysvascular disease, trauma, malignancy, and PJI)? (3) What are the temporal trends in the relative contribution of different etiologies to AKA?

## Materials and Methods

The Nationwide Inpatient Sample (NIS) from 1998 to 2013 was utilized for this study [19]. Our institutional review board deemed this study exempt from approval because it used nonidentifiable information obtained from a public source. Diagnosis and procedure information was captured using International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification codes. The NIS is a stratified probability sample designed to approximate 20% of all community, nonfederal, short-term hospitals in the United States [19]. It is the largest all-payer database and contains information about inpatient hospital admissions such as patient demographics, International Classification of Disease, 9<sup>th</sup> Revision (ICD-9) procedure and diagnosis codes, insurance information, hospital data, length of stay, discharge dispositions, and total charges. As a result of its sampling design, it allows for estimation of procedural volumes at the national level, which is unique to this database.

Selection of the study population followed an algorithm based on previously published studies (Fig. 1) [7, 13, 47]. At first, all adult patients (18 years and older) discharged with a primary or secondary procedure code for AKA were identified using ICD-9 procedure code 84.17. Then, all AKAs were grouped into one of the following five etiologies in a sequential manner using ICD-9 diagnosis codes: malignancy, PJI, trauma, dysvascular disease (peripheral vascular disease, diabetic, or a combination), and other. Such a sequential manner was utilized because patients can have multiple diagnosis codes. For example, a patient undergoing AKA for PJI can have diabetes or peripheral vascular disease as a comorbid condition. The order of the etiologies was determined based on the approximate likelihood of one being the primary reason for AKA if multiple diagnoses are simultaneously present. Therefore, malignancy of the lower limb, which is unlikely to be a secondary diagnosis,



**Fig. 1** The figure shows the algorithm used to identify AKAs from different etiologies along with the ICD-9 codes used. HCUP = Healthcare Cost and Utilization Project.

was chosen first and so on. AKAs resulting from PJI were identified using diagnosis code 996.66. Because specific ICD-9 procedure/diagnosis codes for TKA-related AKA

or PJI of the knee were not available, the AKAs with a diagnosis code for PJI were assumed to be from an infection-related complication of TKA. Demographic and

hospital-related information was recorded for all AKAs (Table 1).

The incidences of AKAs were obtained by dividing the number of AKAs by the annual US adult population (18 years and older) obtained from the US Census Bureau [46]. The proportion of AKAs resulting from each etiology was also evaluated for each year by dividing the number of AKAs resulting from each etiology by the total number of AKAs.

### Statistical Analysis

Discharge weights are provided in the NIS, which allow estimation of national trends. The number of AKAs in the entire nation is obtained by totalling the weights provided with each discharge and accounting for the complex survey design of NIS. Poisson regression analysis was used to analyze whether there was an annual increase in the incidence of the AKAs as a result of the count nature of the

**Table 1.** Demographics of patients undergoing above-knee amputations by etiology

Variable	All etiologies (N = 454,823)	Malignancy (N = 3441)	Periprosthetic joint infection (N = 7708)	Trauma (N = 5028)	Dysvascular (N = 416,740)	Others (N = 11,906)
Age (years)						
18-44	4%	31%	5%	31%	3%	13%
45-64	25%	24%	33%	29%	24%	33%
65-80	41%	31%	45%	21%	42%	36%
> 80	30%	14%	18%	18%	31%	19%
Sex						
Male	52%	59%	49%	62%	51%	56%
Female	48%	41%	51%	38%	49%	44%
Race						
White	47%	58%	65%	56%	46%	56%
Black	23%	9%	9%	14%	24%	13%
Hispanic	7%	10%	5%	7%	7%	4%
Other	3%	3%	2%	4%	3%	2%
Missing	20%	20%	19%	19%	20%	25%
Insurance						
Medicare	78%	44%	74%	42%	80%	63%
Medicaid	8%	13%	7%	12%	8%	12%
Private	11%	33%	15%	28%	9%	17%
Other	3%	9%	5%	17%	3%	7%
Missing	0%	0%	*	0%	0%	0%
Location						
Rural	13%	6%	8%	8%	13%	11%
Urban nonteaching	39%	17%	34%	27%	40%	30%
Urban teaching	47%	77%	57%	64%	46%	57%
Missing	0%	0%	1%	1%	0%	1%
Region						
Northeast	18%	15%	15%	16%	19%	15%
Midwest	20%	22%	26%	20%	20%	23%
South	49%	38%	41%	50%	49%	47%
West	13%	26%	18%	14%	12%	15%
Size						
Small	10%	8%	10%	6%	10%	8%
Medium	25%	18%	23%	22%	25%	22%
Large	65%	74%	66%	71%	64%	69%
Missing	0%	0%	1%	1%	0%	1%

\*Cells with frequency < 11 are suppressed as a result of requirements in the Healthcare Cost and Utilization Project data use agreement.

dependent variable. The population was used as an offset term in the regression model. The changes in the incidence of AKAs are represented using incidence rate ratios (IRRs) with IRR >1 denoting an increase in the procedural volume. The IRR denotes the change in the number of AKAs per 1 million adults per year (incidence of AKA in 1 year divided by the incidence in the preceding year). Linear regression analysis was used to study the annual changes in the proportion of AKAs resulting from different etiologies including PJI. Because the number of AKAs resulting from different etiologies differed in magnitude, normalization was performed when plotting the annual changes in the number of AKAs for better visualization. Statistical analyses were performed with SAS software version 9.3 (Cary, NC, USA). Ninety-five percent confidence intervals (CIs) were calculated. All of the p values were two-tailed, and a value of < 0.05 was considered statistically significant.

**Results**

From 1998 to 2013, the incidence of AKAs decreased by 47% from 174 to 92 AKAs per 1 million adults (IRR [ie, change in the number of AKAs per 1 million adults per year], 0.96; 95% CI, 0.96-0.96; p < 0.001). There were 454,823 AKAs performed in the United States between 1998 and 2013. The annual number of AKAs decreased from 35,594 AKAs in 1998 to 22,260 AKAs in 2013 (Table 2).

From 1998 to 2013, the annual incidence of AKAs resulting from PJI (IRR, 1.07; 95% CI, 1.06-1.07; p < 0.001; Tables 3, 4) and malignancy (IRR, 1.01; 95% CI, 1.00-1.02; p = 0.007) increased; there was no change in the incidence of AKAs related to trauma (IRR, 1.00; 95% CI, 0.99-1.00; p = 0.088), whereas those from dysvascular causes (IRR, 0.96; 95% CI, 0.95-0.96; p < 0.001) and other causes (IRR, 0.97; 95% CI, 0.96-0.97; p < 0.001) decreased (Fig. 2). Compared with 1998, the incidence of AKAs from PJI (in the population) was higher in 2013 (by 263%), whereas that resulting from dysvascular diseases (by 50%), malignancy (by 17%), trauma (by 26%), and other etiologies (by 44%) was lower in 2013 (Fig. 3).

PJI (coefficient = 0.18; 95% CI, 0.15-0.22; p < 0.001), trauma (coefficient = 0.13; 95% CI, 0.09-0.18; p < 0.001), and malignancy (coefficient = 0.04; 95% CI, 0.03-0.05; p < 0.001) increased in relative contributing etiologies to AKA, whereas dysvascular disorders decreased (coefficient = 0.18; 95% CI, 0.15-0.22; p < 0.001) (Table 5). There was no change in the relative contribution from other etiologies (coefficient = 0.02; 95% CI, -0.01 to 0.05; p < 0.226). Of the 35,594 AKAs performed in 1998, 33,140 (93%) were the result of dysvascular causes, 1088 (3%) were the result of trauma, 202 (0.6%) were the result of PJI,

**Table 2.** National estimates of annual volumes of above-knee amputations performed in the United States from 1998 to 2013

Year	US adult population (in millions)	Annual volumes	Annual incidence (per 1 million US adults)
1998	205	35,594	174
1999	207	33,374	161
2000	210	32,992	157
2001	212	32,426	153
2002	215	31,541	147
2003	217	31,654	146
2004	220	31,035	141
2005	222	27,737	125
2006	225	28,431	127
2007	227	26,267	116
2008	230	25,686	112
2009	233	23,728	102
2010	235	24,044	102
2011	238	25,474	107
2012	240	22,580	94
2013	243	22,260	92

and 178 (0.5%) were the result of malignancy. Of the 22,260 AKAs performed in 2013, 19,605 (88%) were the result of dysvascular causes, 960 (4%) were the result of trauma, 870 (4%) were the result of PJI, and 175 (0.8%) were the result of malignancy (Table 3).

**Discussion**

AKA is associated with severe impairment in quality of life and high mortality [38]. PJI is a serious complication of TKA, which may lead to AKA when infection cannot be controlled and/or severe bone or soft tissue loss precludes limb salvage treatments [14, 41]. Historically, the majority of AKAs were considered to be the result of vascular disease, diabetes, trauma, and malignancy with PJI not usually considered a major cause of AKA [47]. Previous studies have found that the risk of AKA after an infected TKA is decreasing [42]. However, given the substantial increase in the volumes of TKA, the national trends in the incidence of AKAs from PJI in the population are unclear. The present study used the NIS database and found that the overall number of AKAs in the United States decreased by 47% from 1998 to 2013. The incidence of AKAs from dysvascular disease has substantially decreased, whereas those from trauma and malignancy have remained fairly constant. However, the incidence of AKAs related to PJI almost quadrupled since 1998. As a result, the proportion of AKAs

**Table 3.** National estimates of annual volumes of above-knee amputations performed in the United States for various etiologies

Year	Malignancy	Periprosthetic joint infection	Trauma	Dysvascular	Others
1998	178	202	1088	33,140	986
1999	186	201	842	31,404	741
2000	157	298	832	30,904	801
2001	158	344	753	30,400	771
2002	243	326	866	29,328	778
2003	224	392	862	29,472	704
2004	217	475	987	28,490	866
2005	196	474	1018	25,237	812
2006	201	581	822	25,901	926
2007	221	442	1038	23,898	668
2008	275	700	1033	22,982	696
2009	226	593	923	21,381	605
2010	255	527	1057	21,479	726
2011	299	663	962	22,914	636
2012	230	620	985	20,205	540
2013	175	870	960	19,605	650

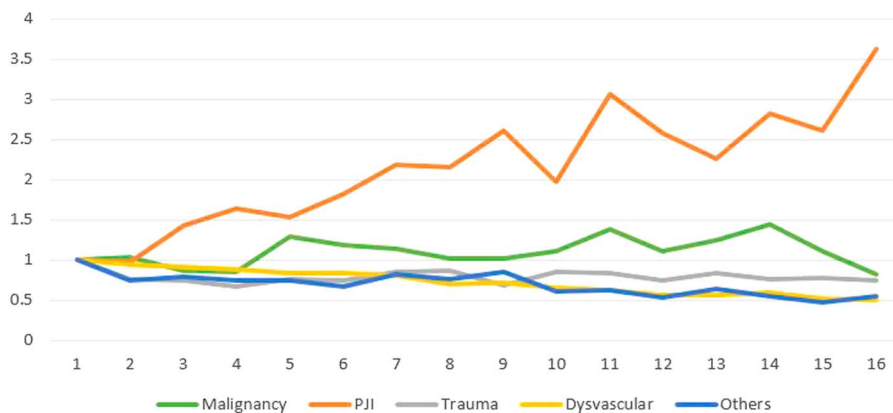
resulting from PJI has increased approximately six times, resulting in the emergence of PJI as a noteworthy cause of AKAs in the United States. Therefore, despite the findings of a decrease in the risk of AKA after a failed TKA by Son et al. [42], the present study found an increase in the overall number of AKAs performed for PJI in the country.

This study has some notable limitations. AKAs resulting from PJI and other etiologies were identified using ICD-9 procedure and diagnosis codes and might be subject to coding errors [15, 31]. For example, a patient could require AKA for vascular disease and a severe

diabetic foot infection with seeding of a prosthetic joint other than the knee or of a knee prosthesis on the contralateral side. Although rare, such instances are possible and might have been erroneously classified as AKAs from PJI in this study. Although national joint registries in countries such as the United Kingdom, Canada, and Australia allow the monitoring of outcomes of all TKAs at a national level, a national registry was not available in the United States [2, 21, 36]. Therefore, an administrative database like NIS was used for estimating national trends in line with other investigators [11, 25, 27]. Although

**Table 4.** Incidence of above-knee amputations in the United States resulting from various etiologies (per 1 million adults)

Year	Malignancy	Periprosthetic joint infection	Trauma	Dysvascular	Others
1998	1	1	5	162	5
1999	1	1	4	151	4
2000	1	1	4	147	4
2001	1	2	4	143	4
2002	1	2	4	137	4
2003	1	2	4	136	3
2004	1	2	5	130	4
2005	1	2	5	114	4
2006	1	3	4	115	4
2007	1	2	5	105	3
2008	1	3	4	100	3
2009	1	3	4	92	3
2010	1	2	4	91	3
2011	1	3	4	96	3
2012	1	3	4	84	2
2013	1	4	4	81	3

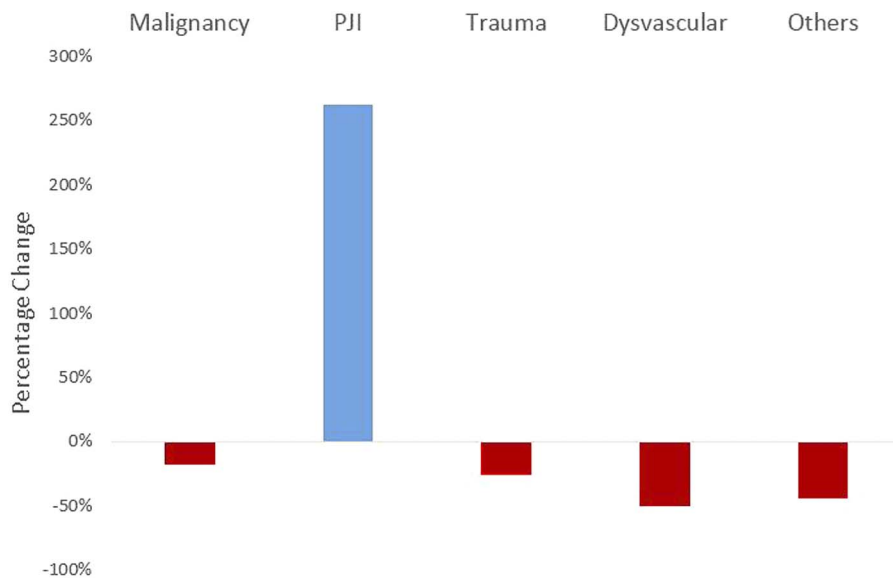


**Fig. 2** The figure shows the annual trends in the incidence of AKAs resulting from various etiologies. The volumes have been normalized to 1998 values for comparison across etiologies.

coding errors can be present in the NIS, it is the largest available national database and provides reliable estimates of the national-level incidence of various procedures or conditions. Because patients undergoing AKA can have multiple etiologies, a sequential method was used to classify the patients into different etiologies, and so some patients might have been misclassified into a wrong category. However, because the approach was similar for all years, and because the study evaluated the yearly changes in etiologies, this is unlikely to affect the conclusions of the study.

The incidence of AKAs from all causes in the United States is declining. The declining trends of AKAs have been previously reported [17, 23, 33]. In a study of Medicare beneficiaries between 1996 and 2011, Goodney

et al. [17] found that the incidence of AKAs declined from 91 to 47 AKAs per 100,000 Medicare patients. The incidence of AKAs (from all causes) reported in our study is higher than that reported in their study, probably because their study included only Medicare patients, whereas our study included all adults in the United States. However, an earlier study, which evaluated the trends in major and minor limb amputations from 1988 to 1996 using the NIS database, showed an increasing incidence of amputations, including AKAs [7]. Although our study did not analyze data before 1998, it is possible that the decline in the incidence of AKAs started in the late 1990s [10]. Similar to other studies, the majority of the AKAs in this study were a result of dysvascular causes [17, 23, 33]. Because a substantial decrease in the incidence of dysvascular



**Fig. 3** The figure shows the percentage change in the incidence of AKAs from 1998 to 2013 resulting from various etiologies.

**Table 5.** Proportion of above-knee amputations resulting from various etiologies from 1998 to 2013

Year	All etiologies	Malignancy	PJI	Trauma	Dysvascular	Others
1998	100%	1%	1%	3%	93%	3%
1999	100%	1%	1%	3%	94%	2%
2000	100%	0%	1%	3%	94%	2%
2001	100%	0%	1%	2%	94%	2%
2002	100%	1%	1%	3%	93%	2%
2003	100%	1%	1%	3%	93%	2%
2004	100%	1%	2%	3%	92%	3%
2005	100%	1%	2%	4%	91%	3%
2006	100%	1%	2%	3%	91%	3%
2007	100%	1%	2%	4%	91%	3%
2008	100%	1%	3%	4%	89%	3%
2009	100%	1%	3%	4%	90%	3%
2010	100%	1%	2%	4%	89%	3%
2011	100%	1%	3%	4%	90%	3%
2012	100%	1%	3%	4%	89%	2%
2013	100%	1%	4%	4%	88%	3%
Annual changes						
Coefficient* (95% CI)	NA	0.04 (0.03-0.05)	0.18 (0.15-0.22)	0.13 (0.09-0.18)	-0.38 (-0.45 to -0.31)	0.02 (-0.01 to 0.05)
p value	NA	< 0.001	< 0.001	< 0.001	< 0.001	0.226

\*Coefficient of linear regression for yearly trends; PJI = periprosthetic joint infection; CI = confidence interval; NA = not applicable.

amputations was found in our study and previous studies, it is not surprising to see a decrease in the overall incidence of AKAs [17, 23, 33].

AKAs resulting from most etiologies such as vascular disease, trauma, and malignancy have decreased or remained constant during the study period, whereas a considerable increase in AKAs resulting from PJI was observed. A number of factors might be responsible for the declining rates of dysvascular amputations. Increasing awareness about amputations along with an emphasis on early screening and detection of vascular disease in patients at risk for amputation may be partly responsible for the decline in amputation rates [16, 30]. Additionally, improvements in revascularization procedures and aggressiveness of reconstructive surgeries might have also contributed to the declining trends of vascular-related amputations in recent years [8, 16]. Similarly, with the implementation of simple and effective interventions such as diabetes self-management education and targeted foot screening programs, the rate of lower extremity amputation in persons with diabetes declined by 47% from 2000 to 2010 [35, 43, 45]. Unfortunately, the declining trends of other etiologies of amputations were accompanied by rising numbers of AKAs resulting from PJI, probably related to the rising number of TKAs and the stable revision burden [26, 28].

This study found that an increasing proportion of AKAs performed in the United States are the result of PJI. Using the NIS, Ziegler-Graham et al. [47] estimated the

prevalence of major lower extremity amputations in the United States was approximately 600,000 in 2005 with vascular disease and diabetes responsible for approximately 80% of the major lower limb amputations followed by trauma and cancer-related amputations. All other etiologies including congenital anomalies and orthopaedic implant failures contributed to < 3% of all the amputations. This is consistent with the results of the current study, which estimated AKAs resulting from PJI were < 3% for year 2005. However, given the projected increase in TKA, PJI can become a major cause of limb loss in the coming years [27]. PJI, which was responsible for only < 1% of the AKAs in 1998, was accountable for 4% of the AKAs in 2013, a more than six times increase during the 16-year period. If these trends continue unaltered, and if this increase is projected to the coming years, more than one-fifth of AKAs in 2030 could be the result of PJI. Because previous studies have projected a substantial increase in the volume of infected TKAs, the number of AKAs related to PJI is also expected to increase [27, 29].

In summary, we found that the incidence of AKAs has declined in the United States. AKAs related to dysvascular disease decreased by half, whereas those resulting from etiologies such as trauma and malignancy have remained fairly constant. However, AKAs performed as a result of PJI more than tripled since 1998. Dysvascular disease is the leading cause of AKA, but PJI appears to be emerging as an important etiology of AKAs in the United States.



Given the increased resource utilization associated with limb loss, the results of this study suggest that national efforts to reduce disability should prioritize PJI. Because the demand for TKA is expected to further increase, PJI could emerge as an important reason for limb loss. Given the increased resource utilization associated with limb loss, further studies are required to evaluate the risk factors for AKA from PJI and to formulate better strategies to manage PJI.

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