Published in final edited form as:

Diabetes Res Clin Pract. 2015 November ; 110(2): 147–157. doi:10.1016/j.diabres.2015.09.016.

High burden of diabetic foot infections in the top end of Australia: An emerging health crisis (DEFINE study)

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Abstract

Introduction—The risk of diabetes mellitus is increasing worldwide, and is particularly high in Indigenous Australians. Complicated foot infection is one of the most common sequelae of diabetes. We describe the incidence and associations of Indigenous and non-Indigenous inpatients with diabetic foot infections at Royal Darwin Hospital.

Methods—All adult Royal Darwin Hospital inpatients with diabetic foot infections were enrolled prospectively from September 2012 to November 2013. Incidence, demographics, microbiology, management and clinical outcomes were analysed by Indigenous status, and association with methicillin resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

Results—There were 245 separate hospital admissions in 177 patients with an incidence of 79 admissions per 100,000 person years. Patients occupied a mean of 19.4 hospital beds each day. Compared to the non-Indigenous population, Indigenous patients had a greater incidence of admission (Rate Ratio (RR) = 5.1, [95%CI = 3.8, 7.0]), were younger (mean difference of 11.1 years; $p < 0.001$), and more likely to undergo major and minor amputations (RR = 4.1 [95%CI = 1.6, 10.7], and 6.2 [95%CI = 3.5, 11.1] respectively). Non-multiresistant methicillin resistant *S.*

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Authors contribution

RC, CR, DG, JD and RP assisted in study design. RC and CR assisted in data collection. RC, JD and RP assisted in analysis of data. RC, CR, DG, JD and RP assisted in writing the manuscript. All authors have approved the final manuscript.

Conflict of interest

None declared.

aureus was present in 44.7% of wounds from Indigenous patients versus 20.6% of non-Indigenous patients (Odds Ratio (OR) = 3.1, [95%CI = 1.5, 6.4]), whereas *P. aeruginosa* presence was significantly lower (15.8% versus 46.0%; OR = 0.22; [95%CI = 0.11, 0.45]). Methicillin resistant *S. aureus* or *P. aeruginosa* infections were associated with longer antibiotic courses and durations of stay.

Conclusions—This study highlights a rising burden of diabetic foot infections in the Top End of Australia, with a four-fold increase in bed days since 2002 and an overrepresentation in the Indigenous population.

Keywords

Diabetes mellitus; Diabetic foot infection; Indigenous; Australia; Methicillin resistant *Staphylococcus aureus*; *Pseudomonas aeruginosa*

1. Introduction

Diabetes mellitus represents a major healthcare concern in both the developed and developing world. By 2030 it is estimated that 552 million people worldwide will have diabetes mellitus; this figure has been updated several times, the latest estimate being over 50% higher than estimates a decade ago [1]. Australia has not escaped the epidemic. The Australian Diabetes and Obesity Study suggested that over 1.4 million Australians (7.4%) had diabetes in 2000, of whom almost a half were undiagnosed [2,3]. By 2033, up to 3.5 million Australians are expected to suffer from this chronic disease [4].

The rates of diabetes mellitus and its complications occur more commonly and at an earlier age in marginalised populations [6]. Indigenous Australians remain a disadvantaged population with significantly poorer health outcomes compared to non-Indigenous Australians [7,8]. Indeed recent studies highlight that between 3.5 and 33.1% of Indigenous adults have diabetes [9], with the DRUID study finding a prevalence of 19.4% in adults aged 15 years and older who lived in and around Darwin, Australia [10].

Diabetic foot ulceration and infection are the most poorly funded and managed of the common complications affecting the cardiovascular system, kidneys, eyes and feet [11]. Diabetic foot ulcers become infected in approximately half of cases [12], with amputation required in over 15% [13]. Foot infections are the most common diabetes related complication requiring hospitalisation [14], and are now the most common cause of lower limb amputation worldwide [15]. They are associated with long hospital stays, the acquisition of multidrug resistant organisms and an enormous financial burden [11,16–18].

Treatment of diabetic foot infections requires multidisciplinary care involving multiple health professionals [19]. Living in remote communities makes access for primary and secondary ulcer prevention and management difficult. These issues are evident at the Royal Darwin Hospital (RDH), where diabetic foot infections are a common presentation. It is over ten years since the last review of diabetic foot infections at RDH, which found high rates of major and minor amputations in this unique Australian population [20], where over a quarter of individuals identify as Indigenous [21].

The DiabEtic Foot Infections in NorthErn australia (DEFINE) study aimed to prospectively assess the incidence, demographics, microbiology, management and outcomes of Indigenous and non-Indigenous inpatients with diabetic foot infections at Royal Darwin Hospital. Secondary aims included subgroup analysis of inpatients with isolation of and infection from methicillin resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*.

2. Methods

2.1. Study design

This prospective study was performed at the RDH between September 2012 and November 2013. Ethics approval was granted by the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (HREC-2012-1843). A portable electronic device was used to collect data on inpatients with diabetic foot infections, using a custom-designed structured electronic data form created in a commercial database (Bento 4, Filemaker, Inc.).

Data were collected during weekly diabetic foot rounds or upon review of patients by the diabetic foot nurse specialist or infectious diseases registrar between these rounds. Patient files and records were followed up and reviewed if discharge did not occur on the day of the diabetic foot round to ensure data were complete. No data were included beyond the date of study cessation.

2.2. Setting

Royal Darwin Hospital is a 367-bed teaching hospital in the Northern Territory, in tropical northern Australia (latitude 12.5° S), of which 64 are acute general surgical beds. It serves as a referral hospital for patients with diabetic foot infections requiring multidisciplinary care in the Top End of the Northern Territory, which in 2013 included an estimated 192,680 people over an area of 500,000 km². It is estimated that 25.9% of the population are Indigenous [21].

The diabetic foot team at RDH consists of nurse specialists, general and vascular surgeons, an infectious diseases registrar, and an orthotist and prosthetist, who undertake weekly multidisciplinary rounds on inpatients.

2.3. Participants

All inpatients 18 years old and over with a diabetic foot infection, as defined by the Infectious Diseases Society of America (IDSA) criteria [22], were eligible to be enrolled in the study. Patients with non-infected ulcers were excluded from the study, as were those with infections resulting from complications acquired during their hospital stay, such as pressure ulcers.

Inpatients were identified on referral to the diabetic foot team. Patients with diabetes at RDH with ulcers or foot infections are referred to this team for management and follow up. There are no other foot management services within the hospital, assisting in the identification of most potential study participants. Patients requiring surgery for diabetic foot infections from peripheral hospitals in the Top End are routinely referred to RDH for this surgery.

2.4. Explanatory variables

Baseline explanatory variables covered domains of demographics and comorbidities. Demographic variables identified from the electronic medical record included date of birth, gender, Indigenous status and home address which was recorded as Darwin, rural Top End, interstate or overseas.

Comorbidity data were recorded if they appeared in the patients' medical admission and progress notes or electronic past medical record. Variables included chronic kidney disease, dialysis, peripheral vascular disease, hypertension, hypercholesterolemia, ischaemic heart disease, alcohol excess, prior amputation(s) and HbA1c. If information was discrepant it was verified with the patient. Chronic kidney disease was also recorded if eGFR was <90 mL/min/1.73 m² consistently on prior laboratory investigations. Peripheral vascular disease was not systematically assessed clinically but was also recorded if identified on invasive or non-invasive angiography during admission. If not identified in the medical record, alcohol excess was defined as greater than two standard drinks per day for men or women daily [23]. Prior amputations were also recorded if identified on physical examination, which was performed for every patient. The most recent HbA1c within the past year was recorded.

2.5. Outcome variables

Outcome variables assessing disease extent included severity of disease on initial presentation and presence of osteomyelitis. The presence and severity of the diabetic foot infection was classified at admission according to the IDSA classification scheme, which divides potential diabetic foot infections into uninfected, mild, moderate and severe categories [22]. These categories correlate with the International Working Group on Diabetic Foot (IWGDF) classification categories from 1 to 4 [14]. Osteomyelitis was considered present if there was consistent histology or microbiology from sterile bone biopsy or resection, if radiology suggested probable or definite osteomyelitis, if a clinical probe to bone test was positive or if the patient was treated for osteomyelitis by the treating clinician.

Microbiological specimens were classified into two types: (i) non-sterile specimens including superficial or deep sinus swabs and (ii) sterile specimens including pus or tissue collected under sterile operative conditions. Microbiology specimens with multiple organisms are frequently reported by the RDH laboratory as cutaneous or enteric flora without further identification. Isolation of *S. aureus*, *P. aeruginosa* and *Burkholderia pseudomallei* were always reported, and to ensure validity of results only these bacteria are analysed in the results.

Given that empiric antibiotic therapy may need to consider recently isolated organisms, isolation of pathogens from foot wounds in the 12 months prior to study entry were recorded. Pathogens recorded included methicillin sensitive *S. aureus* (MSSA), MRSA (divided into non-multiresistant MRSA (nmMRSA) and multiresistant MRSA (mMRSA)), *P. aeruginosa* and *B. pseudomallei*.

Analysis of culture results considered (i) isolation of the pathogen from foot wounds in the 12 months prior to study entry, (ii) isolation of the pathogen from foot wounds during the

study and (iii) isolation of the pathogen from foot wounds during the study period or in the 12 months prior. Subgroup analyses for MRSA and *P. aeruginosa* associations were performed on the third combined group. Further subgroup analyses were performed for MRSA and *P. aeruginosa* infections, defined as isolation from sterile specimens during the study period.

Outcome variables for management during the admission were recorded from the patients' progress notes and electronic medical record including: admission and discharge date, duration, delivery and type of antibiotics, surgical procedures, radiological investigations, review by specialist units, hyperbaric oxygen therapy, use of a total contact cast, ICU admission, Hospital In The Home utilisation and death. Planned duration of antibiotics prescribed at discharge were included in antibiotic duration, until the date of study cessation.

The length of stay was calculated from admission and discharge dates, excluding time spent in the Hospital In The Home program. Surgical procedures were recorded by procedure type and anatomical location. Minor amputations were considered to be amputations below the ankle with major amputations consisting of below and above knee amputations. Antibiotic costs were obtained from the Royal Darwin Hospital Pharmacy. Patients were assumed to be on standard doses of antibiotic therapy according to Therapeutic Guidelines: Antibiotic version 14 [24] for the purposes of cost calculation.

2.6. Statistical analysis

Data were de-identified and analysed using SPSS Statistics for Mac v21 (IBM Corp, Armonk, NY, USA). Categorical variables were described by frequency and numerical variables were described by central tendency and dispersion depending on normality assumptions. Pearson chi square and Fisher's exact test were used to assess relationships between categorical variables. Independent Student's T test and Wilcoxon test assessed relationships between categorical and numerical variables depending on normality. Odds ratios compared categorical percentages, while rate ratios compared incidence rates.

Denominator data for population incidence, including the Indigenous population, were calculated using population figures for 2013 from the Australian Bureau of Statistics (ABS) [21]. Readmissions of the same individual were excluded from incidence of admission calculations. Due to the lack of an accurate estimate for diabetes prevalence amongst the study population, overall population incidence was calculated rather than incidence per head of population with diabetes.

3. Results

During the 14-month study period, there were 264 hospital admissions in 195 individuals with diabetic foot infections. Of these, 18 patients with 19 admissions were excluded: 15 had no apparent infection, one did not have diabetes, and two had neither infection nor diabetes. Of the 177 patients included in the study 26.0% presented two or more times and there were 245 total admissions.

3.1. Baseline characteristics

Demographics, disease severity and comorbidities are documented in Table 1. The mean age of the 177 patients included in the analysis was 54.4 years (95%CI = 28.8, 80.1), and they were predominantly male (106 [60%]) and Indigenous (114 [64%]). Overall 79 (44.6%) were living in Darwin, and 89 (50.3%) lived in the rural Top End, the remaining nine (5.1%) patients were from interstate or another country.

All but seven patients had type II diabetes mellitus, the remainder having type 1 diabetes mellitus. In the 147 patients in whom an HbA1c was available, the median value was 8.8% (IQR = [7.0%, 11.4%] (73 mmol/mol (IQR = [53, 101])). Most patients had evidence of moderate or severe disease, with 41 (23.2%) initially diagnosed with severe infection and 82 (46.3%) with moderate infection.

3.2. Comparison by Indigenous status

Compared to non-Indigenous patients, Indigenous patients were more likely to be female (Odds Ratio = 4.6 (95%CI = 2.2, 9.4)) and younger (50.5 years (95%CI = 28.3, 72.6) versus 61.6 years (95%CI = 36.1, 87.1); $p < 0.001$) (Table 1). Indigenous patients had significantly higher HbA1c levels compared to non-Indigenous patients ($p = 0.027$).

The incidence of admission in the Indigenous population serviced by the Royal Darwin Hospital was 195 per 100,000 person years compared to 38 per 100,000 person years in the non-Indigenous population (RR = 5.1 [95%CI = 3.8, 7.0], $p < 0.0001$). The overall major amputation incidence was 7.6 per 100,000 person years and the minor incidence was 24 per 100,000 person years. The Indigenous major amputation incidence was over four times the non-Indigenous incidence (17.1 versus 4.2 per 100,000 person years; RR = 4.1 [95%CI = 1.6, 10.7], $p = 0.004$). Minor amputation incidence was 63.5 per 100,000 person years in the Indigenous population and 10.2 per 100,000 person years in the non-Indigenous population (RR = 6.2 [95%CI = 3.5, 11.1], $p < 0.0001$). Additional management and outcomes of the two patient groups are presented in Table 2.

3.3. Microbiology

A total of 295 non-sterile superficial and deep wound swabs were collected from the 177 patients on different days with an additional 143 sterile specimens collected from 94 patients on different days (multiple samples on the same day were not counted). There was a median of 2 samples collected per patient (range 0–11).

Table 3 documents the culture results for foot wounds during the study and for 12 months prior to study entry. *S. aureus* was identified in 71.8% (127/177) of patients over this period. Methicillin resistant *S. aureus* was identified in 43.5% (77/177) of patients during this time with 83.1% (64/77) involving nmMRSA, 32.5% (25/77) mMRSA and 15.6% (12/77) both. During the study MRSA was detected from non-sterile specimens in 26% (46/177) of patients compared to 11.9% (21/177) from sterile specimens. Compared to those without MRSA, MRSA isolation was associated with significantly more operations, more major amputations, a longer duration of stay in hospital, a greater number of days of antibiotic use (specifically intravenous antibiotics) and a higher cost of intravenous and oral antibiotics

(Table 4). Methicillin resistant *S. aureus* infection according to presence on sterile operative specimens during the study period was also associated with all these features, in addition to more minor amputations, increased intensive care use and increased oral antibiotic duration (Table 4).

P. aeruginosa was found in 26.6% (47/177) of people during the study and the 12 months prior to study entry. It was present in 17.5% (31/177) of non-sterile specimens and 6.2% (11/177) of sterile specimens during the study. Both patients with *P. aeruginosa* isolated prior to or during the study from sterile and non-sterile samples, and patients who only had *P. aeruginosa* infections (isolated from sterile specimens) during the study period, had longer durations of stay in hospital, greater numbers of days of antibiotic use and increased costs of antibiotics. While patients with *P. aeruginosa* infections had more operations neither group was associated with a risk of increased amputations (Table 5).

3.4. Antibiotic use

Prolonged outpatient antibiotic therapy was necessary in 11.8% (29) of patients who were administered antibiotics through the Hospital In The Home program. Antibiotics were prescribed to patients for a total of 9014 days during the study (median of 33 days [IQR = 16, 67.5] per patient), including 5099 days with intravenous antibiotic therapy and 4272 days with oral therapy. The median cost of antibiotics was \$969 (AUD) per person [IQR = 398, 2071] with the majority of this attributable to intravenous antibiotics. The total cost of intravenous antibiotics was \$285,752 compared to \$13,446 for oral antibiotics.

3.5. Clinical outcome

The median duration of hospital stay was 29 days (range 0–307, [IQR = 12, 48.5]) days, with a total bed occupancy of 8275 hospital bed-days. In total, patients with diabetic foot infections occupied a mean of 19.4 hospital beds each day, equivalent to 31.1% of the available adult surgical beds. The median number of medical units involved in a patient's care was three [range 1–10].

During the study period 303 operations were performed on 138 patients (78.0%), the number of operations ranging from zero to eight per person. Twenty-six percent (14/54) of patients who underwent one minor amputation required a second minor amputation on the same side with 10 of 54 (19%) who underwent one minor amputation requiring a subsequent major amputation. Thirty-five percent of patients who underwent one minor amputation underwent a second minor or major amputation on the same side.

In total there were four deaths. Two non-Indigenous patients died of severe sepsis secondary to their diabetic foot infections. An Indigenous patient died secondary to an intracranial haemorrhage after a fall in hospital and another Indigenous patient developed hospital acquired pneumonia whilst awaiting nursing home placement after bilateral below knee amputations.

4. Discussion

This 14-month prospective study of inpatients with diabetic foot infections at RDH recorded 177 patients involved in 245 admissions. Indigenous patients were significantly younger, more commonly female and had a higher incidence of major and minor amputations compared to non-Indigenous patients. Foot infections required intensive resources with a median length of stay of 29 days and median duration of antibiotic therapy of 33 days.

The number of hospital bed days has increased four-fold since a previous study at RDH between 1997 and 2000 which found a total of 5377 bed-days, compared to 8275 bed-days during the current fourteen month study [20]. As such, patients with diabetic foot infections utilise 19.4 hospital beds every day at RDH or 31% of surgical beds. The previous study by O'Rourke et al. [20] included all diabetic patients with non-infective as well as infective foot disease. Hence the increased bed occupancy attributable to diabetic foot infections in our analysis is likely to be a conservative estimate.

The increase in bed days for patients admitted with diabetic foot infections is not surprising given the rising incidence of diabetes mellitus in Australia and the world [1,5]. The pressure on hospital beds and the healthcare budget is only likely to further increase over the coming years. If we assume an increase at the same rate over the next 12 years, we will see close to 80 RDH beds filled with patients with diabetic foot infections every day in 2025 (27% of current acute hospital beds).

This increase in bed occupancy does not appear to be related to increased duration of hospital admission. In the current study the median duration of stay was 29 days and similar to other Australian studies, although direct comparison is difficult due to variations in inclusion criteria and analysis. The Fremantle Diabetes Study (1993–1996) found a median length of stay of 24 days for diabetic patients undergoing lower extremity amputations [17]. The study of O'Rourke et al., at the Royal Darwin Hospital between 1997 and 2000, reported a mean of 44 days, but this was for inpatients with any diabetic foot disease [20]. Steffen et al. reported a similar mean duration of hospitalisation of 48 days at Cairns Base Hospital between 1992 and 1994 [16] in a population of patients admitted for surgical management of diabetic foot disease.

The major amputation incidence is comparable to other developed countries [28], but higher than recent Queensland data which were similar to the non-Indigenous incidence in the current study [29]. The minor amputation incidence reflects Australian data [29,30] that show an increased rate of minor amputations compared to the international figures [31,32]. Similar to retrospective nationwide data there were over three minor amputations for every major amputation, confirming that the previously reported results are consistent in the Top End's context [30].

Using Government data [25] to calculate an amputation incidence for the previous study in the Top End 12 years earlier [20], would estimate the major amputation incidence at around 6 per 100,000 person years, similar to the current study's incidence of 7.6 per 100,000 person years. However, the minor amputation incidence has risen from around 5.5 in the previous study to the current figure of 24 per 100,000 person years. The change to more

conservative surgical approaches is further reflected in the high rate of patients requiring a second minor amputation (26%) or a major amputation (19%) following their first minor amputation. Such trends indicate the importance of following the minor amputation rate as well as the major amputation rate [30]. Given the high rate of reoperation these people require especially intensive follow up and intervention to avoid further ulcers, infection and amputation.

Admissions are over-represented in the Indigenous population with 195 admissions per 100,000 person years. This reflects the previously described higher rate of diabetes mellitus in Indigenous Australians [9] and a higher rate of amputations in Indigenous Australians [16,26,27].

The amputation incidence of the Indigenous population is concerning. The Indigenous population of the Top End had an incidence of major amputation 4.1 times the non-Indigenous population and an even wider gap in minor amputation incidence – 6.2 times the non-Indigenous population. This reflects previous Australian studies from Queensland and Western Australia that have demonstrated the rates of diabetic foot infections and amputations to be disproportionately high in the Australian Indigenous population [16,26,27].

If the increasing rate of diabetes mellitus and its complications are not addressed within the Indigenous population there is a risk that the life expectancy gap will widen again. Not only did Indigenous patients have a higher admission and amputation incidence, they also presented at a significantly younger age with 35.1% of the cohort undergoing any type of lower extremity amputation. These figures are more concerning, when you consider that the five-year survival following major amputation is as low as 28–31% and can be worse if there is renal failure or more proximal amputations [33,34].

There is a desperate need for government to heed the increasing calls for funding to manage diabetic foot complications [11]. Prevention of diabetic ulcers in primary care centres through increased patient and provider education including Indigenous Health Workers may play a role in conjunction with other evidence-based interventions [35], although a Cochrane review did not demonstrate that education alone reduces diabetic foot ulcers [36]. A 2003 study found only 35–59% of Indigenous people with diabetes mellitus received the recommended yearly foot check [37]. Currently there are very few podiatrists servicing rural communities in the Top End [38], which we believe provides reduced ability to prevent ulcers, to identify complications early in high risk patients, or to provide offloading orthotic devices or specialised footwear outside of the private health system.

Systematic strategies including primary healthcare screening, education, podiatric involvement, use of multidisciplinary teams and evidence-based pathways can reduce hospitalisations and amputation rates by up to 90% [39,40]. We believe the introduction of additional interventions adapted to the Top End, where in our experience patient adherence can be poor, would facilitate this reduction. Suitable measures include directly observed oral therapy, greater use of ambulatory intravenous therapy, increased use of total contact casts and phone message reminders. The increased use of total contact casts in Indigenous

patients in the current study probably reflects an adaptation to diabetic foot infection management in the Top End, through an attempt by clinicians to ensure pressure offloading and wound protection despite the risks of using casts in infected ulcers [41].

Microbiological diagnosis for diabetic foot infections is ideally made through sterile collection of tissue specimens with evidence of infection microbiologically [41]. In the current study this was not always undertaken, highlighting the difficulty of robust diagnosis. Additional recognised factors that limit microbiological comparison in diabetic foot infections [42] include the complex microbiological environment of the diabetic foot [43] and varied reporting techniques [41]. We chose to focus our analysis upon the two most important pathogens, *S. aureus* and *P. aeruginosa*, which are usually reported in a standard format [44] and are thus more easily comparable between studies and over time.

MRSA was identified in 43.5% of patients, one of the highest rates identified in the international literature [45], although this figure includes MRSA identified in the preceding 12 months, whereas other studies generally only recorded organisms isolated during the study period. Furthermore we could not confirm if MRSA identified in the previous 12 months was from the same or a different foot wound. Compared to Australian studies, this is a greater frequency than a study from Southern Australia, which found MRSA in 24% of inpatients [43] but is similar to a study from Northern Queensland where 39.3% of tested patients had MRSA [16]. The majority of patients in the current study with MRSA had nmMRSA and this was more prevalent in Indigenous patients (44.7% overall (51/114) and 92.7% of patients with MRSA (51/55)).

In comparison to nmMRSA, *P. aeruginosa* was identified in a very high proportion of non-Indigenous patients (46.0%), suggesting different factors leading to colonisation and infection with these two organisms. Non-multiresistant methicillin resistant *S. aureus* is recognised to be common in remote Indigenous communities in the Northern Territory [46], which may explain its prevalence in the Indigenous population with diabetic foot infections. This contrasts to many previously described diabetic foot cohorts where *S. aureus* was less common in warm, tropical climates [45].

Studies of patients with diabetic foot infections vary regarding the association between MRSA and poor clinical outcomes [45]. Despite this, MRSA has been previously associated with prolonged wound healing [47], prolonged hospitalisation [48], clinical failure [49,50], increased amputation risk [51] and increased morbidity [52]. This study provides supportive evidence for poorer outcomes in patients infected with MRSA. There was a significant association between MRSA infection and prolonged length of stay, increased duration and cost of antibiotic therapy and increased numbers of amputations and operations.

P. aeruginosa was associated with prolonged length of stay and prolonged duration of antibiotic therapy in the current study. This correlates with findings by another Australian study that demonstrated *P. aeruginosa* to be more common in chronic wounds [43] and may reflect colonisation of chronic wounds over time. Other studies had also previously found *P. aeruginosa* to be associated with poorer outcomes [53,54] which may be due to an ability to

impair wound healing [55], although it remains unclear whether *P. aeruginosa* is truly a causative factor in poor outcomes.

Conclusions drawn from this study are limited by its observational nature. Associations between Indigenous status and age or length of stay, antibiotic therapy and microbiological infection do not prove causation. Figures from this study are likely to underestimate the true incidence of diabetic foot infections in the Top End with some patients being managed at Darwin Private Hospital or admitted to remote hospitals such as in Katherine or Nhulunbuy, although nearly all foot surgery occurs at RDH. In addition, the study does not consider outpatient management, where the majority of patients with mild infections are managed and it only includes diabetic foot infections without considering the significant morbidity caused by other diabetic foot disease.

Our study is likely to have captured the majority of inpatients with diabetic foot infections in the Top End of the Northern Territory. However the single-centre setting limits the generalisability of our conclusions. Furthermore, analysis of only major pathogens and a high proportion of non-sterile specimens in the current study limit comparison of the microbiology results to other studies reporting less common pathogens.

In conclusion, this prospective study demonstrates an increasing incidence in diabetic foot infections and their associated morbidity in the Top End, with a concerning discrepancy between the Indigenous and non-Indigenous populations. This epidemic is associated with a rapidly increasing healthcare burden, which is likely to worsen unless strategic planning can be implemented to address the issue. Diabetes mellitus and its complications, such as lower limb amputations, are more common in Indigenous Australians, and the ongoing increase in diabetic foot infections poses a major health threat to this population at a time when other health indices are narrowing between Indigenous and non-Indigenous Australians [56,57].

Acknowledgements

We would like to thank the entire Royal Darwin Hospital diabetic foot team who have been involved in this project; collecting data and caring for patients. Thank you to Dr Sarah Huffam for her suggestions and to Alan Staples and Joanna Kelly for their assistance in determining patient costs.

Funding

There was no external funding source for this study.

Abbreviations

ABS	Australian Bureau of Statistics
AUD	Australian dollars
CI	confidence interval
DEFINE	DiabEtic Foot Infections in NorthErn australia
IDSA	Infectious Diseases Society of America
IQR	interquartile range

IWGDF	International Working Group on Diabetic Feet
mMRSA	multiresistant methicillin resistant <i>Staphylococcus aureus</i>
MRSA	methicillin resistant <i>Staphylococcus aureus</i>
MSSA	methicillin sensitive <i>Staphylococcus aureus</i>
nmMRSA	non-multiresistant methicillin resistant <i>Staphylococcus aureus</i>
OR	odds ratio
RDH	Royal Darwin Hospital
RR	rate ratio
SD	standard deviation

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Table 1

Baseline assessment of 177 consecutive Indigenous and non-Indigenous inpatients with diabetic foot infections from Royal Darwin Hospital between September 2012 and November 2013.

	Total <i>n</i> = 177	Indigenous <i>n</i> = 114	Non-Indigenous <i>n</i> = 63	<i>p</i> -value
No. of patients (%)				
Demographics				
Age (mean (95% confidence interval))	54.4 (28.8, 80.1)	50.5 (28.3, 72.6)	61.6 (36.1, 87.1)	<0.001
Male gender	106 (59.9)	55 (48.2)	51 (81.0)	0.001
Live in Darwin	79 (44.6)	30 (26.3)	49 (77.8)	0.001
Disease severity				
Severe disease on initial presentation	41 (23.2)	30 (27.2)	10 (15.9)	
Osteomyelitis present	63 (35.6)	41 (36.0)	22 (34.9)	
Comorbidities				
HbA1c (%) (median [interquartile range])	8.8 [7.0, 11.4]	9.3 [7.3, 11.6]	7.8 [6.3, 10.2]	0.027
HbA1c (mmol/mol) (median [IQR])	73 [53, 101]	78 [56, 103]	62 [45, 88]	0.027
Chronic kidney disease	77 (43.5)	59 (51.8)	18 (28.6)	0.003
Haemodialysis	20 (11.3)	16 (14)	4 (6.3)	
Known peripheral vascular disease	37 (20.9)	15 (13.2)	22 (34.9)	0.001
Hypertension	96 (54.2)	63 (55.3)	33 (52.4)	
Hypercholesterolaemia	61 (34.5)	39 (34.2)	22 (34.9)	
Ischaemic heart disease	50 (28.2)	27 (23.7)	23 (36.5)	
Alcohol excess	48 (27.1)	35 (30.7)	13 (20.6)	
Prior amputation(s)	50 (28.2)	38 (33.3)	12 (19.0)	0.043

Table 2

Management and outcomes of consecutive inpatients with diabetic foot infections from Royal Darwin Hospital.

	Total <i>n</i> = 177	Indigenous <i>n</i> = 114	Non-Indigenous <i>n</i> = 63	<i>p</i> -value ^{<i>a</i>}
No. of patients (%) ^{<i>b</i>}				
Management				
ICU admission	20 (11.3)	14 (12.3)	6 (9.5)	
No. of people with minor amputations	54 (30.5)	37 (32.5)	17 (27.0)	
No. of people with major amputations	17 (9.6)	10 (8.8)	7 (11.1)	
Total no. of operations per person ^{<i>c</i>}	1 [1, 3]	1 [1, 3]	1 [0, 2]	0.013
Use of total contact casts	52 (29.4)	43 (37.7)	9 (14.3)	0.001
Hyperbaric oxygen therapy	27 (15.3)	19 (16.7)	8 (12.7)	
Hospital In The Home	23 (13.0)	17 (14.9)	6 (9.5)	
Bacterial identification ^{<i>d</i>}				
MRSA ^{<i>e</i>}	77 (43.5)	55 (48.2)	22 (34.9)	
nmMRSA ^{<i>f</i>}	64 (36.2)	51 (44.7)	13 (20.6)	0.001
mMRSA ^{<i>g</i>}	25 (14.1)	14 (12.3)	11 (17.5)	
<i>Staphylococcus aureus</i>	127 (71.8)	85 (74.6)	42 (66.7)	
<i>Pseudomonas aeruginosa</i>	47 (26.6)	18 (15.8)	29 (46.0)	<0.001
Antibiotics				
Duration of antibiotics (days) per person ^{<i>c</i>}	33 [16, 67.5]	37.5 [17, 69.75]	21 [14, 56]	
Duration of intravenous antibiotics ^{<i>c</i>}	19 [9, 37]	20 [10, 41.25]	14 [7, 33]	
Duration of oral antibiotics ^{<i>c</i>}	13 [1.5, 38.5]	14 [2, 42]	13 [0, 26]	
Cost of antibiotics per person ^{<i>c,h</i>}	969 [398, 2071]	1075 [406, 2210]	776 [374, 1969]	
Cost of intravenous antibiotics ^{<i>c,h</i>}	953 [373, 1931]	1067 [378, 2080]	743 [371, 1697]	
Cost of oral antibiotics ^{<i>c,h</i>}	8.4 [0, 28]	8.6 [1, 28]	5.6 [0, 25]	
Admission outcomes				
Length of stay (days) per person ^{<i>c</i>}	29 [12, 55.5]	34 [12, 57]	21 [11, 43]	
Deaths	4 (2.3)	2 (1.8)	2 (3.2)	

^a Comparison of Indigenous versus non-Indigenous patients.

^b Number of patients and percentage of total 177 patients unless otherwise stated.

^c Median and interquartile range.

^d Isolation of bacteria from foot wounds during the study or in the 12 months prior to study entry.

^e Methicillin resistant *Staphylococcus aureus*.

^f Non-multiresistant methicillin resistant *Staphylococcus aureus*.

^g Multiresistant methicillin resistant *Staphylococcus aureus*.

^h Australian dollars.

Table 3

Isolation of key pathogens from 177 consecutive inpatients with diabetic foot infections from Royal Darwin Hospital between September 2012 and November 2013.

Pathogen	Isolated prior to admission ^a (%)	Isolated during admission ^b (%)	Isolated prior to or during admission ^c (%)
MRSA ^d	39 (22)	54 (30.5)	77 (43.5)
nmMRSA ^e	34 (19.2)	37 (20.9)	64 (36.2)
mMRSA ^f	6 (3.4)	21 (11.9)	25 (14.1)
MSSA ^g	71 (40.1)	35 (19.8)	81 (45.8)
<i>Pseudomonas aeruginosa</i>	13 (7.3)	37 (20.9)	47 (26.6)
<i>Burkholderia pseudomallei</i>		2 (1.1)	

^a Number of patients that had the pathogen isolated from foot wounds within 12 months prior to study entry.

^b Number of patients that had the pathogen isolated during the study period from a foot wound.

^c Number of patients that had the pathogen isolated from foot wounds during the study period or in the 12 months prior to study entry.

^d Methicillin resistant *Staphylococcus aureus*.

^e Non-multiresistant methicillin resistant *Staphylococcus aureus*.

^f Multiresistant methicillin resistant *Staphylococcus aureus*.

^g Methicillin sensitive *Staphylococcus aureus*.

Table 4Comparison of inpatients with diabetic foot infections with isolation^a of MRSA^b and infection^c from MRSA.

	MRSA isolation n = 77	No MRSA isolation n = 100	p-value	MRSA infection n = 21	No MRSA infection n = 156	p-value
	No. of patients (%) ^d			No. of patients (%) ^d		
Age (years) ^e	53.9 (27.9, 80)	54.8 (29.3, 80.3)		56.3 (78.0, 34.6)	54.2 (28.0, 80.4)	
HbA1c (%) ^{f,g}	8.8 [7.0, 11.8]	9.1 [6.9, 10.8]		8.2 [7.0, 11.8]	9.1 [7.0, 11.3]	
HbA1c (mmol/mol) ^{f,g}	72 [53, 105]	76 [52, 95]		66 [53, 105]	76 [53, 100]	
Severe infection	20 (26)	21 (21)		6 (28.6)	35 (22.4)	
Management						
ICU Admission	13 (16.9)	7 (7)		6 (28.6)	14 (9)	0.018
No. of people with minor amputations	27 (35.1)	27 (27)		13 (61.9)	41 (26.3)	0.001
No. of people with major amputations	14 (18.2)	3 (3)	0.001	6 (28.6)	11 (7.1)	0.007
Total no. of operations per person ^g	2 [1, 3.5]	1 [0, 2]	<0.001	3 [2, 4.5]	1 [0.25, 2]	<0.001
Use of total contact casts	22 (28.6)	30 (30)		9 (42.9)	43 (27.6)	
Hyperbaric oxygen therapy	16 (20.8)	11 (11)		5 (23.8)	22 (14.1)	
Hospital In The Home	14 (18.2)	9 (9)		3 (14.3)	20 (12.8)	
Antibiotics						
Antibiotic duration per person (days) ^g	52 [19.5, 93.5]	22 [14, 48]	<0.001	68 [42, 141.5]	30.5 [15, 58.75]	<0.001
Intravenous antibiotic duration (days) ^g	29 [13.5, 51.5]	13.5 [7, 29.75]	<0.001	49 [18.5, 97.5]	17.5 [8, 33]	<0.001
Oral antibiotic duration (days) ^g	16 [0, 43.5]	10.5 [3, 21.75]		33 [10.5, 74]	11 [1, 30.75]	0.01
Antibiotic cost per person ^{g,h}	1435 [764, 3989]	639 [326, 1488]	<0.001	3431 [1186, 5334]	896 [380, 1736]	<0.001
Intravenous antibiotic cost per person ^{g,h}	1339 [682, 3495]	636 [318, 1479]	<0.001	3431 [1067, 5259]	876 [368, 1697]	<0.001
Oral antibiotic cost per person ^{g,h}	16.8 [0, 101]	5.6 [1, 16]	0.002	55.4 [9.2, 451.2]	5.6 [0.3, 23.0]	0.001
Admission outcomes						
Length of stay (days) per person ^g	42 [18.5, 114]	21 [8.25, 36]	<0.001	68 [32.5, 136]	26 [10.25, 42]	<0.001

^aPatients that had MRSA isolated from foot wounds during the study period or in the 12 months prior to study entry.^bMethicillin resistant *Staphylococcus aureus*.^cPatients that had MRSA isolated from sterile operative specimens from foot wounds during the study period.^dNumber of patients and percentage of total patients unless otherwise stated.^eMean and 95% confidence interval.^fData missing for 30 patients.^gMedian and interquartile range.^hAustralian dollars.

Table 5

Comparison of inpatients with diabetic foot infections with isolation^a of *P. aeruginosa*^b and infection^c from *P. aeruginosa*.

	<i>P. aeruginosa</i> isolation n = 47	No <i>P. aeruginosa</i> isolation n = 130	p-value	<i>P. aeruginosa</i> infection n = 11	No <i>P. aeruginosa</i> infection n = 166	p-value
	No. of patients (%) ^d			No. of patients (%) ^d		
Age (years) ^e	61.5 (35, 88)	51.9 (28.4, 75.4)	<0.001	60.4 (41.3, 79.6)	54.0 (28.2, 79.9)	
HbA1c (%) ^{f,g}	7.5 [6.2, 11.3]	9.2 [7.3, 11.4]		7.2 [6.4, 12.9]	8.9 [7.0, 11.3]	
HbA1c (mmol/mol) ^{f,g}	59 [44, 100]	77 [56, 101]		55 [46, 118]	73 [53, 100]	
Severe infection	12 (25.5)	29 (22.3)		3 (27.3)	38 (22.9)	
Management						
ICU Admission	8 (17)	12 (9.2)		2 (18.2)	18 (10.8)	
No. of people with minor amputations	17 (36.2)	37 (28.5)		5 (45.5)	49 (29.5)	
No. of people with major amputations	7 (14.9)	10 (7.7)		3 (27.3)	14 (8.4)	
Total no. of operations per person ^g	1 [1, 3]	1 [1, 2]		3 [1, 5]	1 [1, 2]	0.009
Use of total contact casts	9 (19.1)	43 (33.1)		6 (54.5)	46 (27.7)	
Hyperbaric oxygen therapy	7 (14.9)	20 (15.4)		3 (27.3)	24 (14.5)	
Hospital In The Home	10 (21.3)	13 (10.0)	0.049	2 (18.2)	21 (12.7)	
Antibiotics						
Antibiotic duration per person (days) ^g	50 [29, 86]	27.5 [14.75, 62]	0.003	93 [52, 139]	32 [15, 62]	<0.001
Intravenous antibiotic duration (days) ^g	29 [15, 48]	17 [7.75, 33]	0.004	44 [23, 86]	18 [8.75, 34]	0.004
Oral antibiotic duration (days) ^g	24 [2, 53]	11.5 [1, 26.5]		51 [32, 71]	11.5 [1, 32]	0.001
Antibiotic cost per person ^{g,h}	1420 [851, 2426]	847 [1745, 352]	0.003	2064 [1420, 5729]	943 [393, 1915]	0.015
Intravenous antibiotic cost per person ^{g,h}	1379 [707, 2411]	843 [349, 1698]	0.006	1944 [1379, 5000]	902 [371, 1749]	0.015
Oral antibiotic cost per person ^{g,h}	16 [0, 160]	6 [0, 21]		40.4 [15.8, 408.6]	5.7 [0.2, 25.7]	0.003
Admission outcomes						
Length of stay (days) per person ^g	41 [16, 108]	25.5 [10, 44]	0.002	57 [37, 149]	27.5 [11, 46]	0.012

^aPatients that had *P. aeruginosa* isolated from foot wounds during the study period or in the 12 months prior to study entry.

^b*Pseudomonas aeruginosa*.

^cPatients that had *P. aeruginosa* isolated from sterile operative specimens from foot wounds during the study period.

^dNumber of patients and percentage of total patients unless otherwise stated.

^eMean and 95% confidence interval.

^fData missing for 30 patients.

^gMedian and interquartile range.

^hAustralian dollars.