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ORIGINAL RESEARCH

Trends in Hospitalization for Tuberculosis and Other Opportunistic Infections in Australian Patients with Inflammatory Joint Diseases

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ABSTRACT

Objective: As immune-modulating therapy has become the standard of care for idiopathic inflammatory joint diseases (IJD), we investigated whether this has changed the rates for hospitalization with opportunistic infections (OI).

Methods: Administrative longitudinal statewide health data identified patients hospitalized at least twice with diagnostic codes for rheumatoid arthritis (RA, $n = 7730$), psoriatic arthritis (PsA, $n = 529$) or axial spondylarthritis (AS, $n = 1126$) in Western Australia in the period 1985–2015. Overall incidence rates/1000 person-years (IR with 95% CI) for microbiologically confirmed OI (mycobacterial, fungal, and viral infections) during 180,963 person-years were analyzed across 10-year periods with IR trend rates analyzed by least square regression (R^2) for all IJD categories.

Results: A total of 2584 OI occurred with higher IR rates observed in RA (15.34, CI 14.71–15.99) than PsA (8.73, CI 7.14–10.56) and AS (10.88, CI 9.63–12.24) patients ($p < 0.001$). IR rates were highest for *Candidiasis* across all three IJD categories (IR 10.0 vs. 6.32 vs. 6.88, respectively), while Varicella-zoster (VZV) was most frequent non-candida OI (IR 2.83.0 vs. 1.50 vs. 1.49, respectively) followed by mycobacterial (IR 1.14 vs. 0.08 vs. 0.24, respectively) and other mycotic infections (IR 0.60 vs. 0.58 vs. 0.86, respectively). Over time, the IR for tuberculosis and pneumocystosis decreased and remained stable for VZV infections in RA patients, but IR for all other OI increased across all disease categories. OI admission associated with 6.5% (CI 5.6–7.5) in-hospital mortality.

Conclusions: Despite decreasing admission rates for tuberculosis and pneumocystosis in RA patients, an overall increase in mycotic and viral infection rates over time was seen across all three IJD. Together with a significant case fatality rate, this indicates continued efforts are needed to improve OI prevention in the management of IJD patients.

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Keywords: Opportunistic infections; Rheumatic diseases; Biologicals

Key Summary Points

A decrease in hospitalization rates for tuberculosis and pneumocystosis occurred over three decades for Australian patients with rheumatoid arthritis. However, TBC rates remain above population level.

In contrast, over that time period, rates for non-tuberculosis mycobacterial, mycotic infections, and *Cytomegalovirus* (CMV) infections requiring hospitalization increased, while Zoster infection rates remained stable for patients with rheumatoid arthritis.

For patients with psoriatic arthritis and ankylosing spondylitis, overall TBC incidence rates remained low, but both *Candida* and non-candida opportunistic infections rates increased over time.

Candidiasis was the most prevalent opportunistic infection followed by Zoster infections across all three disease categories.

Hospitalization for any opportunistic infections was associated with a 6.5% in-hospital mortality rate.

INTRODUCTION

The management of patients with immune-mediated inflammatory joint diseases (IJD) has changed dramatically over the last 30 years during which methotrexate became the established anchor drug for peripheral arthritis followed by an ever-increasing arsenal of cytokine and kinase-inhibiting drugs [1–3]. Methotrexate use in rheumatoid arthritis (RA) patients has doubled in the last three decades, while subsidized biological therapy with etanercept became available for RA patients in Australia in 2003, followed by subsequent approval for use in other IJD and for other TNF inhibitors (2004, 2010, 2014), rituximab (2007), abatacept (2008) and tocilizumab (2010) [4]. This more intense treatment approach provides valuable symptomatic relief and protection against joint complications, but also predisposes the patient to side effects, including infections [5]. Multiple studies have analyzed rates of severe bacterial infections in IJD [6–9], but there are only limited data on opportunistic infections (OI), which mainly stem from clinical trials. Exposure time during clinical trials is usually limited, whereas IJD patients typically require longer-term immune-modulating therapy that places patients at risk of OI over a protracted period of time. Registry-based studies from Europe and the USA reported OI rates between 152 and 3000 per 100,000 for various IJD [10, 11] with the wide range due to heterogeneity in patient selection, differences in defining OI (e.g., in- or exclusion of herpes zoster) and regional influences as tofacitinib use in Asia led to double the H. zoster rate seen in Europe [12]. Population-based studies, which are less prone to selection bias and allow long-term follow-up, can improve our understanding of the scarcity of data on OI for specific IJD [8, 13–15]. Based on the above, we performed a study to investigate the rate of overall and IJD-specific hospital admission rates for OI among patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) across Western Australia (WA) over the period 1985–2014 when early more intensive immunomodulation for IJD gradually became embedded in clinical practice.

METHODS

This population-based retrospective observational study used prospectively collected, statewide longitudinal administrative health data for IJD patients as recorded in the Western Australian Rheumatic Disease Epidemiological Registry (WARDER). WARDER data were extracted and linked through the Western Australian Data Linkage System (WADLS), which covers all public and private hospitals in

Western Australia (WA) (pop 2.5 million) and applies probabilistic matching to provide individual longitudinal health data across the Hospital Morbidity Data Collection (HMDC), WA Cancer Registry, WA Mortality Registry or the Emergency Department Data Collection (EDDC) for registered IJD patients.

We selected patients with prevalent IJD defined as having at least two International Classification of Diseases (ICD-9-CM or ICD-10-AM) diagnostic codes separated by at least 30 days for one of the three defined IJD (rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) (suppl Table 1) in the HMDC between January 1, 1985 and December 31, 2014. This algorithm has demonstrated accuracy in identifying patients with various inflammatory rheumatic diseases [16–18].

Opportunistic infections (OI) were defined as a microbiologically confirmed infection with the pathogen of interest (suppl Table 1) registered in HDMC. Included infections were tuberculosis (TBC) and nontuberculous mycobacterial infections (NTMB), fungal infections (candidiasis, aspergillosis, cryptococcosis, histoplasmosis), pneumocystosis, and viral infections (varicella-zoster virus (VZV), *Cytomegalovirus* (CMV). This selection of OI follows the EULAR recommendations for reporting OI during surveillance studies and is consistent with data presented in an earlier meta-analysis [11, 18].

Study entry was at the first-ever hospital contact for each patient, while index admission was the first IJD-related admission. Primary outcomes were OI incidence rates per 1000 person-years (IR) for all OI across IJD categories, temporal trends over 10-year periods for specific OI within each IJD category and in-hospital (30 days) as well as all-cause mortality per 1000 person-years (MR) based on date of death in WA Death Registry during subsequent follow up. Comorbidity was calculated using a modified Charlson comorbidity index (mCCI), that excluded the scores for rheumatic disease (weighted score 1) to minimize confounding with mCCI at index hospitalization based on accumulated health data from prior hospital separations. The Human Research Ethics Committee at the WA Department of Health considered this project to be of low risk and waived the need for individual consent given the use of deidentified data and approved this project (WADOH HREC # 2016.24).

Statistical analyses descriptive statistics include median and interquartile range (IQR) for continuous variables compared by non-parametric methods (Kruskal–Wallis), categorical data described with a frequency and proportion and group comparisons tested with odds ratios (OR) and Fisher's exact test. OI incidence rates were calculated per 1000 person-years with 95% CI derived from Poisson distribution and compared across disease categories by incidence rate ratios using conditional maximum likelihood estimates [19]. Changes in OI rates over time were assessed by (a) linear least squares regression analysis using the coefficient of determination (R-squared, R^2) as the goodness-of-fit measure, where higher coefficients indicate a better fit for increasing or decreasing incidence rates and (b) analysis of variance (ANOVA) to compare mean IR values across three decades. Mortality rates (MR) per 1000 person-years were compared across categories by mortality rate ratios with 95% confidence intervals. All analyses were performed using SPSS software v23.0 (IBM, USA) and OpenEpi software with two-sided p values (p) < 0.05 considered to be statistically significant.

RESULTS

Descriptive characteristics of patients with RA (n = 7330), PsA (n = 529), and AS (n = 1126) (Table 1) showed age and gender distribution within the expected range for each IJD category with a relatively underrepresentation of patients identifying as Indigenous (population prevalence at 3.5%) and a higher frequency of baseline comorbidity observed in PsA patients. There was no clear trend in any of six comorbid conditions including diabetes mellitus in each IJD category over time (Suppl. Figure 1).

During almost 20 years of follow-up across all IJD categories, OI occurred more often in RA (17.9%) than PsA (12.6%) or AS patients (13.3%)

Table 1 Patient characteristics at index hospitalization across the three categories of inflammatory joint disease. Figures indicate frequency (%) or median (interquartile range) unless otherwise stated

	RA (n = 7330)	PsA (n = 529)	AS (n = 1126)
Female	5151 (70.3)	289 (54.6)	454 (40.3)
Age at index hospitalization	63 (50–74)	50 (38–62)	47 (34–60)
Indigenous Australian	102 (1.4)	6 (1.1)	< 5 (0.3)
Private insurance	2545 (34.7)	209 (39.5)	442 (41)
mCCI at index hospitalization (mean/SD)admission (IQR)	1 (0–1)	2 (0–2)	1 (1–1)
Nr with CCI > 0 at index hospitalization	4189 (57.6)	394 (73.3)	827 (73.4)
Follow–up (months)	239 (141–340)	235 (136–302)	289 (191–366)

RA rheumatoid arthritis, *PsA* psoriatic arthritis, *AS* ankylosing spondylitis, *OI* opportunistic infection, *95% CI* 95% confidence interval, *mCCI* modified Charlson Comorbidity Index score (excludes rheumatic disease), *ICU* intensive care unit

(p = 0.002) with a significantly higher overall OI incidence rate in RA patients than in PsA and AS patients (both $p < 0.01$) while the rate difference between PsA and AS was borderline significant (p = 0.05) (Table 2). Over the three study decades, the rate of overall OI increased in all three disease categories (Fig. 1A).

Analysis of specific OI demonstrated that candidiasis was the most frequent OI by number and with significantly increasing rates over time across all three IJD categories (Table 3, Fig. 1B). Candidiasis was more frequent in female patients with RA (14.9 vs. 12.1%, $p < 0.01$), PsA (13.5 vs. 6.3%, $p < 0.01$) and AS (14.5 vs. 7.1%, $p < 0.01$) but age at *Candida* diagnosis did not differ by gender in each IJD (all $p > 0.1$). Rates for non-*Candida* OI also rose over time across all categories (Fig. 1C). *TBC* hospitalization was rare in PsA, while in RA and AS hospitalization for TBC declined but rates for *NTBM* increased (Suppl Fig. 1). The TBC incidence rate in the latest decade was still higher than the population background rate of TBC in WA [20]. Overall, non-*Candida* mycotic infection rates increased in all categories especially since 2005 (Suppl Fig. 2). Pneumocystosis occurred in RA patients only pre-2005, while Cryptococcus incidence rates increased significantly over time in RA patients (IR from 0.02 to 0.63, R^2 0.75, p = 0.13); aspergillosis incidence also increased in RA (IR from 0.22 to 0.50, R^2 0.99, p = 0.004) and nearly doubled in AS (IR from 1.05 to 1.74, 0.72.p = 0.15). Rates for other mycotic infections than above mentioned also rose across all three categories over time (Suppl Fig. 3). VZV infection rates rose over the last decade in AS patients with no significant change seen in RA or PsA patients (Suppl Fig. 4) and with CMV testing not available before 1995, a rate increase was seen in RA and AS patients after 2005.

Patients with OI spent an average between 7 and 11 days in the hospital with longer stays observed in RA patients (Table 2). The need for ICU admission (4.9% overall) and the frequency of in-hospital death (6.4%) did not differ significantly between groups, while long-term mortality rates ratios were increased for patients with OI compared to patients in the same disease category not experiencing OI.

DISCUSSION

This observational study included three decades during which management options and guidelines for IJD patients have changed significantly following the introduction of MTX as anchor drug in the 1990s and targeted biologic drug therapy available in Australia since 2005 [4, 21]. The results of this study indicate that despite

Table 2 Overall frequency, incidence rate per 1000 person-years (95% confidence intervals), and outcome data for patients hospitalized with opportunistic infection (OI) across three categories of inflammatory joint diseases

	RA (*n* = 7330)	**PsA (*n* = 529)**	**AS (*n* = 1126)**
Patients with any OI (%) 38 (6.3) 91 (6.4)	1319 (17.9)	67 (12.6)	135 (13.3)
Total number of *non-Candida* OI	767	30	101
Total number of *Candida* infections	1437	75	174
Total person-years followed	143,653	12,034	25,276
non-*Candida* OI incidence	5.34 (4.97–5.71)*	2.49 (1.71–3.51)	3.99 (3.27–4.83)
Candida incidence rate	10.0 (9.45–10.53)*	6.32 (4.93–7.76)	6.88 (5.91–7.96)
Outcomes all OI admission	*n* = 2106	(*n* = 101)	(*n* = 246)
Length of hospital stay (days)	11 (5–21)	8 (3.5–17)	7 (2–17)
ICU admission	102 (4.7)	5 (4.9)	13 (5.3)
In–hospital death	141 (6.7)	7 (6.9)	11 (4.5)
mCCI last observation	3 (2–6)	3 (2–5)	2 (1–4)
Number with mCCI $\geq$ 2 at last observation	1388 (81.1)	498 (94.2)	715 (63.5)
Mortality rate ratio (95% CI)	1.16 (1.08–1.25)	2.45 (1.68–3.54)	1.82 (1.36–2.40)

Mortality rate ratio is the number of deaths per 1000 observation years in patients with OI compared to patients without OI in same disease category.
RA rheumatoid arthritis, *PsA* psoriatic arthritis, *AS* ankylosing spondylitis
Low numbers are given as < 5 due to HREC requirements

significant reductions in incidence rates for TBC and pneumocystosis in RA patients, the hospitalization rates for all other OI have increased in RA, PsA, and AS patients with the steepest increases seen since 2005.

RA has been the most widely studied IJD in terms of serious and opportunistic infections since the start of the biological therapy era [22]. The overall non-*Candida* OI rate in RA patients in this study fits well with the 5.6/1000 incidence of serious OI requiring admission reported from Spain [23]. In a meta-analysis of clinical trials, the recalculated overall OI rate was 3.3/1000 person-years (96 OI among 32,504 patients over 24 weeks) in the period 1998–2012, with a higher rate observed in patients on biological drugs compared to placebo or sDMARD [24]. A recently reported study from Korea, which used less stringent OI definitions and included outpatient visits, reported an OI rate of 37.6/1000 in RA patients with minimal change over time [25], while national insurance in- and outpatient data from Taiwan found OI incidence to be 25/1000 person-years in RA patients [26]. Although restricted to inpatient data, our data support this lack of improvement in overall OI rates in RA patients despite the fact that admissions for TBC infection rates decreased over time. This is likely due to prophylactic measures taken in RA patients initiating biologic therapy but other explanations (e.g., increased outpatient treatment for TBC) cannot be ruled out. TBC infections requiring admission in RA patients however still occurred at a rate of 0.38/1000 person-years in the last study decade, which remains significantly higher than the stably low TBC incidence rate of 5–6 cases per 100,000 Australian population [20]. Furthermore, other mycobacterial infection rates increased in that time frame. This increased susceptibility to mycobacterial infections in RA patients has been found across

Table 3 Incidence rates per 1000 person-years for specific opportunistic infections (OI) across three decades in each disease category

OI	IJD	Overall IR	1985–1994	1995–2004	2005–2014	Coefficient R^2	p value (ANOVA)
Candidiasis	RA	10.00	3.60	11.26	16.45	0.988	0.003
	PsA	6.32	2.78	8.14	6.74	0.507	0.380
	AS	6.88	2.24	5.59	11.80	0.970	0.010
TBC	RA	0.54	0.72	0.49	0.38	0.638	0.017
	PsA	0.08	–	0.21	–	0.286	NA
	AS	0.12	0.45	–	0.12	0.211	0.380
NTBM	RA	0.60	0.54	0.52	0.78	0.940	0.210
	PsA	–	–	–	–	0.643	
	AS	0.12	–	–	0.12	0.752	
Cryptococcal	RA	0.21	0.02	0.07	0.63	0.643	0.120
	PsA	–	–	–	–	0.993	
	AS	0.08	–	–	0.23	0.629	
Aspergillosis	RA	0.33	0.22	0.32	0.50	0.722	0.012
	PsA	0.33	–	0.63	0.25	0.874	0.650
	AS	0.90	1.05	0.10	1.74	0.816	0.670
Histoplasmosis	RA	0.01	–	–	0.03	0.787	0.180
	PsA	–	–	–	–	0.314	
	AS	–	–	–	–	NA	
Other mycoses	RA	0.60	0.12	0.41	1.46	0.865	0.050
	PsA	0.58	0.62	0.21	1.00	0.684	0.600
	AS	0.86	–	0.39	2.08	0.949	0.067
Pneumocystosis	RA	0.04	0.06	0.06	–	0.836	0.140
	PsA	–	–	–	–	0.713	
	AS	–	–	–	–	0.643	
VZV	RA	2.83	2.52	3.23	2.69	R2	0.690
	PsA	1.50	2.16	0.42	2.25	0.988	0.830
	AS	1.49	0.15	1.47	2.55	0.507	0.000
CMV	RA	0.18	–	0.13	0.48	0.970	0.031
	PsA	–	–	–	–	0.638	0.128
	AS	0.43	–	0.10	1.16	0.286	0.690

TBC tuberculosis, *NTBM* non-tuberculosis mycobacteria

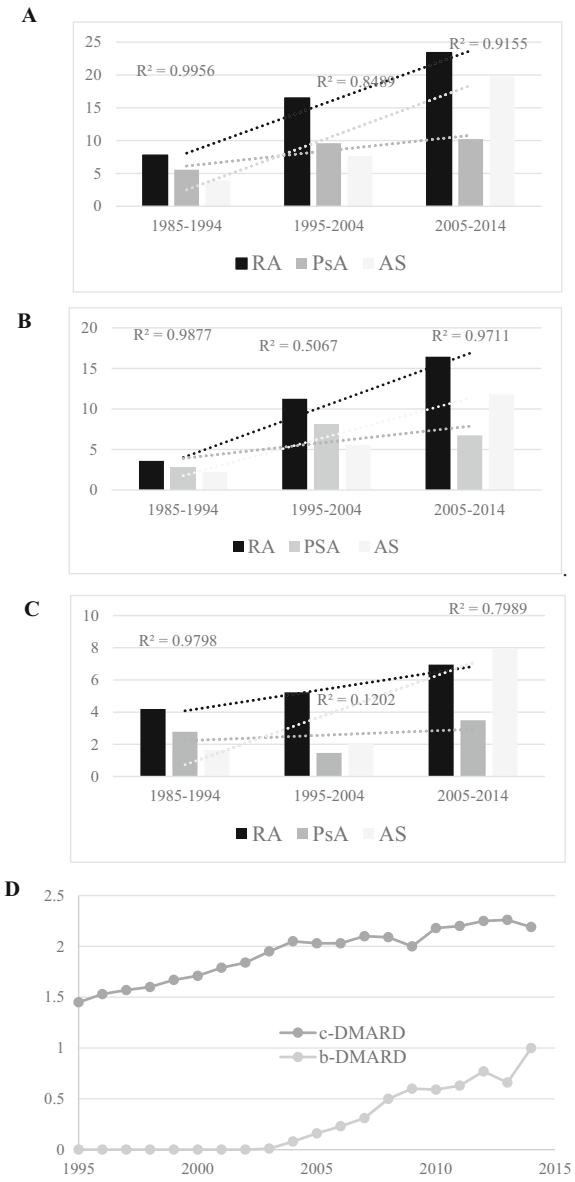

Fig. 1 Incidence rate per 1000 person-years for all opportunistic infections (OI) (**A**), *Candida* (**B**) and non-*Candida* infections (**C**) by joint disease category over time. **D** The increasing usage of conventional (cDMARD) and biological (bDMARD) over two decades in RA patients in Western Australia expressed as defined daily dosage per 1000 individuals (adapted from Ref. 4). *RA* rheumatoid arthritis, *PsA* psoriatic arthritis, *AS* ankylosing spondylitis. *Stippled lines* give trend and coefficient of determination (R^2) by least squares regression analysis. *p* values derived from ANOVA

multiple studies and seems to be due to a poorly defined combination of patient and disease characteristics possibly anti-TNFi therapy [22, 27–30]. While the rate of pneumocystosis admissions pleasingly decreased to zero in the last decade, most likely as a result of increased prophylactic measures [31], the IR of both *Candida* infections and non-*Candida* fungal infections increased over time. While our data predated the introduction of anti-IL17 therapy, candidiasis was also the most frequent fungal OI observed in the Taiwanese national insurance study [26]. *Candida* infections were twice as frequent in female IJD patients and while we were unable analyze this predisposition further, it would suggest increased surveillance for and potential use of *Candida* prophylaxis in female IJD patients. The IR for cryptococcal infections in this study was similar to the 0.22 IR seen in a single center retrospective study from Taiwan where higher risk was observed for patients on biologics [32]. The most frequent viral OI observed in RA patients was VZV (IR 2.8/1000 person-years) in line with IR in other RA studies between 1.6 and 10.9 /100 person-years [27]. Despite the well-known association between VZV and immunosuppressive therapy and the availability of prophylaxis, VZV rates unfortunately did not decline over time. This suggests that clinicians faced significant difficulties in defining important characteristics in estimating and preventing the risk of zoster infections, already before the VZV increase seen following the introduction of Jak inhibitor therapy in 2015 [33, 34].

With limited data on OI rates in PsA and AS patients outside short-term clinical trial results [22, 35], we also analyzed serious OI for these patient groups. Candidiasis was again the most frequent OI observed in both categories and its IR rose significantly over time, especially in PsA patients. With few data on fungal infections available for PsA and AS [36], our data (although from a selected group of PsA and AS patients requiring admission) indicate rising IR for a number of fungal infections in these patients (Table 3) and illustrate that immunomodulating therapy over longer periods of time than observed in trials in these patients groups does increase the risk of OI [37]. No PCP infections

were observed in PsA and AS patients, while mycobacterial infection rates were significantly lower than in RA. A recent pooled analysis of PsA and AS patients treated with secukinumab reported a latent TBC IR over 2 years of 0.02 and 0.08/1000 person-years, respectively, with no cases of active TBC observed [38]. There are few real-life data on zoster in PsA [36], but a recent metanalysis confirmed a lower risk of zoster in PsA than RA and found only a slightly elevated risk of zoster in PsA patients requiring multiple agents for severe disease [39]. A recent systemic review of nine clinical trials demonstrated that VZV risk was higher across multiple biological therapies than in non-biological therapy (odds ratios 1.48 CI: 1.18–1.86 [40]. The rate of VZV in a combined psoriasis/PsA/AS cohort treated with TNF inhibitors was 4.4/1000 person-years [41], like the combined rate (4.8/1000 person-years) reported here in the same study period. While our results support an overall lower risk of OI in PsA/AS patients, they also raise the question of whether safety data from RA studies can be meaningfully extrapolated to PsA and AS patients [42]. Finally, while our data confirm that OI are relatively infrequent complications in the lifelong disease facing IJD patients, they require considerable health care resource (25.696 days spent in the hospital at an average (2020 price) cost of AU$ 2332/day) and more importantly associate with a high case fatality rate.

Limitations for this study include the strict criteria for IJD inclusion, which provided a high specificity [17] but may have reduced the sensitivity. Comparative data from the general population could have clarified whether the observed changes were unique to IJD patients. Also, the use of hospital admission data for OI detection may have led to a selection bias towards more severe OI as OI patients treated on an outpatient basis were not included. The low proportion of Indigenous patients with IJD has been reported before and the lack of shared epitope in the restricted MHC polymorphisms of Australian Aborigines considered as explanation for their apparent resistance to IJD [43]. Increasing awareness of diseases and more advanced laboratory technology may also have confounded our data. Although we found no clear changes in the frequency of comorbid conditions over time, they remain potential risk factors for OI in patients receiving immunomodulating therapy. Finally, whereas the use of ICD-based administrative health data reflects the physician-based diagnoses, more detailed data such as for inflammatory markers, details of specific antirheumatic drug therapy, or anti-infectious treatment were not available. The strengths of this study lie in the large number and population-wide representation of patients with a rare complication, a median follow-up of nearly 20 years to allow trend analysis of OI over time, the comparison between different IJD categories, and the inclusion of infectious disease codes with an unequivocal microbial test result (culture, PCR or other) to ensure a high specificity of the presented OI data.

CONCLUSIONS

Despite improvements in hospitalization rates for TBC and pneumocystosis, we observed a rising incidence rate over three decades for a wide range of other OI requiring hospitalization across all three categories of inflammatory joint disease. This suggests that the more aggressive treatment approach in IJD to achieve disease remission and reduce comorbidity comes at an increasing expense of OI complications. These results indicate the urgent need for wider implementation of preventative measures for OI in IJD.

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designed the study and was responsible for acquisition and analysis of the data and wrote the first draft. HK, DP and CI: contributed to interpretation of the data and were involved in critically revising and approving the final manuscript.

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Compliance with Ethics Guidelines. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Approval for use of de-identified data was obtained from the Human Research Ethics Committee at the WA Department of Health (WADOH HREC#2016.24).

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available as WA Health is proprietor of this administrative health data dataset. The data that support the findings of this study were used under license from WA Health Data Linkage Branch. Restrictions apply to the availability of these data, but upon reasonable request and following permission of WA Health and WA Data Linkage Branch data can be made available from the authors.

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