Title: Drawing attention to a neglected injecting-related harm: A systematic review of AA-amyloidosis among people who inject drugs

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ABSTRACT

Background and Aims

Chronic skin and soft tissue infections (SSTI) among people who inject drugs (PWID) can lead to AA-amyloidosis: a serious, yet neglected, multi-organ disease. We aim to synthesise findings on the epidemiology, risk factors, clinical outcomes, screening recommendations, and challenges to treatment for AA-amyloidosis among PWID.

Methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We searched the following bibliographic databases in July 2017: CINAHL Plus, Embase, Global Health, MEDLINE, PsycEXTRA, PsycINFO, and SCOPUS. Studies were included if they investigated AA-amyloidosis in PWID. Studies were not restricted to location, study type, year, or language of publication. Study heterogeneity precluded meta-analysis (I2: 86%); we present a narrative review of the literature.

Results

Thirty-seven papers from eight countries met inclusion criteria. A total of 781 PWID are reported on, of whom 177 had AA-amyloidosis. Where disease causality is established, it is attributed to chronic inflammation caused by injecting-related SSTIs. Most (88.7%) PWID with AA-amyloidosis had SSTIs.

Proportions of PWID with AA amyloidosis at post-mortem range from 1.6% (Germany) to 22.5% (Serbia). Biopsy studies report from 5.26% (Portugal) to 50% (Germany) of AA-amyloidosis in PWID with suspected or known kidney disease. Following diagnosis, the typical trajectory for PWID with AA-amyloidosis was rapid deterioration of renal function requiring haemodialysis (32.8%). Treatment difficulties, end-stage renal failure (40%), and premature death from sepsis (33%) were observed. Good outcomes, including reversibility of AA-amyloidosis are attributed to rapid treatment of the underlining inflammation and injecting cessation. Notably, given the population in question, no studies were published in addiction or harm reduction journals; most (92%) appear in specialist nephrology and medical journals.

Conclusion

There is strong evidence of an association between skin and soft tissue infections (SSTIs) and AA-amyloidosis. Among people who inject drugs, injecting-related SSTIs are a significant cause of morbidity and premature mortality and there is evidence of increasing SSTI prevalence. Limitations in the literature make it difficult to estimate AA-amyloidosis prevalence among people who inject drugs.

KEYWORDS: AA amyloidosis; kidney disease; people who inject drugs; skin and soft tissue infections; subcutaneous injection; systematic review

INTRODUCTION

A recent systematic review of all injecting-related diseases and injuries among people who inject drugs (PWID) failed to note one serious sequelae of injecting-related skin and soft tissue infections (SSTIs) – AA-amyloidosis (1). AA-amyloidosis is a progressive and often fatal complication of chronic infection and inflammation caused by overproduction of the acute phase protein, serum amyloid A (SAA) (2, 3). SAA deposits in tissues throughout the body; deposition in the kidney is a particular concern. Untreated AA-amyloidosis can lead to renal failure and premature death (4). Up to 10% of patients exposed to sustained concentrations of SAA (typically associated with inflammatory conditions such as rheumatoid arthritis) may develop AA-amyloidosis (5). AA-amyloidosis has, however, become less common in people with rheumatoid arthritis in developed countries due to advances in anti-inflammatory medications (5).

AA-amyloidosis prevalence among PWID may be increasing; though the literature does little to establish prevalence over time. The first documented case is a heroin injector, admitted to a New York hospital in 1963 (6). The first European case, who injected drugs subcutaneously, was admitted to a Spanish hospital in 1986 (7). From the mid 1980's AA-amyloidosis incidence appears to have supplanted that of other renal diseases, such as focal glomerulosclerosis or hepatic glomerulonephritis, among PWID (8-11). In Germany, AA amyloidosis was identified as the predominant cause of progressive kidney disease among PWID in the decade prior to 2012, accounting for 50% of cases, with 21% attributable to glomerulonephritis (8). In London, of AA-amyloidosis cases identified among PWID from 1990 – 2005, 65% occurred in the last five years (11). Glomerulonephritis was not present, despite high rates of hepatitis C infection (95%) in this population. The reasons for this shift are not clear. Posited causes include: increased longevity of the PWID population, HIV infection, increased in subcutaneous injecting (or 'skin-popping') due to limited venous access, and associated increases in SSTIs among PWID (8, 9, 11). Injection of crack cocaine, prevalent and increasing among PWID in the UK (12), may also play a role; given increased

frequency of injecting, numbing of injection sites, venous damage and SSTIs associated with stimulant injection (13).

The evidence for understanding the incidence and prevalence of AA-amyloidosis among PWID is weak with case reports predominant among published articles. Awareness of AA-amyloidosis among practitioners and researchers who work with PWID is low (1). Consequently, we systematically reviewed the literature on AA-amyloidosis among PWID. Our objectives were to: summarise the known epidemiology of AA-amyloidosis among PWID (prevalence, distribution, risk factors, and outcomes); map the history of AA-amyloidosis reports among PWID with attention to geography, time period, report type and audience; explore causal factors for AA-amyloidosis occurrence and outcomes; and provide a synthesis of intervention recommendations as well as any evidence of intervention or treatment implementation and efficacy.

METHODS

Search strategy

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14). We searched eight databases (Africa-Wide Information, CINAHL Plus, Embase, Global Health, MEDLINE, PsycEXTRA, PsycINFO, and SCOPUS) on 5 July 2017 to identify all studies that investigated AA-amyloidosis in PWID. We used combinations of keywords, medical subject headings (MeSH), and search terms for injecting and 'skin-popping' of illicit drugs, and for the condition AA-amyloidosis (Appendix 1). Reference lists were searched and cross-checked to verify that all relevant studies were included in the review.

Eligibility

There were no restrictions applied for language of publication, location, or study type. Reviews and conference abstracts were excluded. Studies were also excluded if they reported on: animal or

experimental studies, other types of amyloidosis or renal diseases, diagnostic criteria or transplantation, amyloidosis associated with diabetes or rheumatoid arthritis.

RB and MH independently assessed all titles and abstracts and potentially eligible full-text manuscripts against eligibility criteria. Where disagreement regarding study inclusion occurred, decisions were reached through discussion with CM.

Data extraction

RB extracted the following data for each study: author, year of publication, journal, study type, sample size, country, patient characteristics, diagnosis and outcome, intervention recommendations, evidence of treatment implementation, and efficacy (Table 1). These data were verified by MH.

Methodological Quality

Two authors (RB/MH) independently assessed the methodological quality of the case series, cohort and cross-sectional studies using the National Institute of Health Study Quality Assessment Tools (15). In the case of discordant assessments RB and MH discussed the studies and came to an agreed rating.

Analysis

A narrative synthesis was conducted across key themes (i.e. epidemiology, risk factors, clinical outcomes, screening recommendations, and challenges to treatment). Meta-analysis was not possible given the heterogeneity of the included studies; however, we conducted a sub-group meta-analysis with inverse variance weights using a random effects model to graphically display a forest plot and to estimate pooled percentages for the proportion of PWID with AA-amyloidosis detected at post-mortem (Appendix 2).

RESULTS

Study Selection

Database searches to 5 July 2017 discovered 875 records; with an additional five records identified from reference lists. After removal of duplicates, 650 titles and abstracts were screened for eligibility. In total, 591 abstracts were excluded as they did not meet the eligibility criteria, and 59 abstracts were selected for full-text assessment. Twenty-two records were excluded as: the full-text was not available (n=10), they did not report on PWID (n=9), they did not report on AA-amyloidosis (n=1), or the record included the same study population as an included study (n=2). Figure 1. Of the 10 studies for which full-text was not available, four were published before 1987. The documents could not be located by the Library & Archives Service, LSHTM). Attempts to contact authors were unsuccessful; several authors had died. In total, 37 studies are included in the following review.

Quality Assessment

All three case series studies (9, 16, 17) were rated as 'good'. Only one paper used a cross-sectional design and was rated as 'fair' (10). Of the five included cohort studies the following were rated as: 'fair' (10, 11, 18), and 'good' (4, 19). The most common reason for a 'fair' rating was lack of blinding of researchers to exposure status, and/or a failure to report sample justification, power description, or variance of effect estimates. Case reports (n=24) were not subject to quality assessment.

Study characteristics

Included studies represented studies conducted in eight countries (Table 1): 24 were conducted in the United States (6, 10, 16-18, 20-38); 12 in Europe (4, 7-9, 11, 19, 39-44), and one in India (45).

INSERT TABLE 1

Type of reports and audience

No articles were published in journals whose aims and scope were related to harm reduction, drug dependency, or addiction. More than half were published in medical or pathology journals (n=21) (4, 6, 11, 16, 17, 20, 24-32, 35-37, 40, 45), with 13 in nephrology journals (7-10, 18, 19, 22, 23, 34, 38,

39, 43, 44) (Table 1). The majority of studies were case reports (n=24) (6, 7, 20-28, 30-32, 34-38, 41-45) or case series (n=3) (9, 16, 17), relating to 59 PWID (Table 2). Five cohort and biopsy review studies (retrospective and prospective) followed a total of 100 PWID from renal biopsy or AA-amyloidosis diagnosis (4, 8, 11, 18, 19). Four post-mortem reviews considered 40 (40), 105 (39), 150 (29), and 292 (33) PWID. One paper presented two cross-sectional studies comprising 35 PWID (10).

INSERT TABLE 2

Epidemiology of AA-amyloidosis among PWID

In total across all studies, 781 PWID were reported on, 177 (22.7%) had a diagnosis of AA-amyloidosis (Table 2). The majority with AA-amyloidosis (157, 89%) had reported evidence of injecting-related SSTI.

Overview of drug injection patterns

PWID with AA-amyloidosis mostly injected heroin solely or in combination with cocaine. Other reported injected drugs included: pentazocine (28, 45), tripelennamine (28), methamphetamine (18), and unspecified drugs (7, 26, 44). The route of injecting was predominantly intravenous, with transitions to subcutaneous once venous access had become problematic. Overall, the duration of reported intravenous injecting spanned from two to 30 years, and subcutaneous from two to 18 years.

Proportion of AA-amyloidosis detected in PWID at post-mortem

Four post-mortem studies, from Germany (39), New York (33), (29), and Serbia (40) provide an indication of the proportion of PWID with AA-amyloidosis in these populations (Table 3). The German study employed a retrospective analysis of all forensic autopsies carried out on 129 illicit drug users from January 2009 to April 2011 in Frankfurt/Main (39). The aim was to examine the impact of illicit drug use on kidney integrity; known cases of pre-existing kidney disease were excluded. The sample included 105 PWID, identified through medical records and examination of

injecting site scars. Deceased persons were predominantly white (92%), median age at death was 39 years, with documented duration of illicit drug use of 17 years. AA-amyloidosis was detected in two people (1.9%), both with HIV.

A study in New York reported prospective data from 150 PWID examined at autopsy for renal amyloidosis from October to December 1981, and in February 1982 (29). Injecting status was determined though toxicology reports, injecting site scars and interviews with relatives. AA-amyloidosis was found in seven individuals (4.7%); all black men, mean age 42 years. A later New York study reviewed all post-mortem data from 1981-1990 at one Harlem hospital, with the aim of assessing hepatic amyloidosis in PWID (33). Of the 292 deceased PWID identified, 12 (4.1%) had AA-amyloidosis in the liver. A substantially higher proportion of AA-amyloidosis in the liver, at 22.5% (n=9), was found at post-mortem among 40 PWID in Serbia (40). No amyloidosis was present in control non-PWID autopsies (n=10). As the liver is a secondary organ impacted by AA-amyloidosis, these two hepatic-focused studies (33, 40) might have missed individuals at an earlier stage of disease. The pooled estimate of the proportion of PWID with AA-amyloidosis from the meta-analysis of post-mortem studies with sample sizes>100 (n=3) was 3% 95% CI (2%, 5%). (Appendix 2)

INSERT TABLE 3

Proportion of AA-amyloidosis detected in PWID with proteinuria

Three studies reported proportions of AA-amyloidosis among living PWID with proteinuria or kidney disease. A New York study investigating renal biopsy outcomes among PWID with proteinuria found AA-amyloidosis in 29% (4/14) of biopsies between 1977-1980 and 48% (10/21) between 1981-1983 (10). In Portugal, between 1993-2001, of 19 PWID receiving biopsies due to proteinuria one (5.3%) had AA-amyloidosis (19). A German biopsy study reports 12 cases (50%) of AA-amyloidosis between 2002-2012 among 24 PWID with renal failure or proteinuria (8). In the UK, 20 cases of AA-amyloidosis among PWID were found during a review of renal biopsy records from 1990-2005 at two London hospitals (11). A similar review, from 1998-2013, at two US hospitals (San Francisco and

Chicago) found 24 cases of AA-amyloidosis, all among PWID (18). For both studies (11, 18), the total number of PWID records reviewed is not provided.

Risk predictions, trend, and geography

Several authors note an increase in AA-amyloidosis prevalence, however no studies were sufficient for trend analysis. In New York (10, 16, 17), the UK (11) and Norway (9) authors reported increased prevalence of AA-amyloidosis among PWID attributable, in part, to increased longevity of drug using populations and shifts in drug injection from venous to subcutaneous (7, 16).

An early study, reviewing renal biopsy findings at three New York Hospitals from 1969-1975, reports four cases of AA-amyloidosis (10%) from 40 PWID with proteinuria (17). This is viewed as noteworthy, given no prior reported cases. A later New York study reports an increase in AA-amyloidosis among PWID receiving renal biopsy from 29% to 48% in the years 1977-1980 to 1981-1983 (10). Focal glomerulosclerosis diagnoses decreased from 57% to 29% - indicating a significant (P=0.025) change in renal disease diagnosis among PWID from 1977 to 1983. In London, numbers of PWID identified with AA-amyloidosis increased from two in 1990–1994, to five in 1995–1999, and 13 in 2000–2005 (11). In Oslo, Norway, nine PWID were diagnosed with AA-amyloidosis between 2005 and 2008; with no evidence of AA-amyloidosis among the PWID population prior to 2005 (9).

Prevalence is geographically variable with all studies except one based in Europe or the US. Geographic disparity is also suggested within a single country. A 2015 US study compares AA-amyloidosis among patients undergoing renal biopsy between 1998-2013 in two hospitals – one in San Francisco, the other in Chicago (18). Of the 425 San Francisco biopsies, 24 led to an AA-amyloidosis diagnosis – all among PWID. No amyloidosis was found among 160 renal biopsies conducted in Chicago despite similar patient demographics.

Risk factors for AA-amyloidosis among PWID

Studies identified potential risk factors for AA-amyloidosis among PWID. These included SSTIs, subcutaneous injection, drug source-form, injection duration, and viral infection.

Skin and soft tissue infections

The most commonly reported risk for AA-amyloidosis among PWID was chronic infection caused by drug injection (4, 6, 7, 9-11, 16, 17, 20, 23, 25, 26, 28-30, 32, 35, 36, 42, 43). Of the total 177 PWID diagnosed with AA-amyloidosis 89% (n=157) were reported to have a history of SSTI. A wide range of SSTIs and other diseases associated with chronic inflammation were documented among PWID participants; particularly those diagnosed with AA-amyloidosis. Extensive injecting-related SSTIs were reported among six of seven PWID with AA amyloidosis in a New York post-mortem study (29). In a German study, 92% of PWID with AA amyloidosis had chronic or repeated SSTIs, compared to 50% of PWID with other renal diseases, p=0.069 (8). The most common SSTIs reported were abscesses, ulcers, cellulitis, and chronic suppurative cutaneous infections.

Subcutaneous injecting ('skin-popping')

AA amyloidosis was more common among PWID who injected subcutaneously ('skin-popping') rather than intravenously. Of the 37 included studies, 24 (65%) reported skin-popping among PWID with AA-amyloidosis. In one New York post-mortem study, 14% (6/44) of those injecting subcutaneously had AA amyloidosis, compared with 1% (1/105) for intravenous injecting (29). Of 24 PWID with AA-amyloidosis in San Francisco, all had transitioned to skin-popping due to venous damage (18). Skin-popping is associated with SSTI; as the nonsterile injection of drug solution into the subcutaneous space increases infection risk (46-48).

Injecting duration and age

Associations between longer duration of injecting and AA-amyloidosis are noted in the review. Of the nine PWID with AA-amyloidosis in the Serbian post-mortem study, seven (78%) had been injecting for five years or more, two (22%) had been injecting for two to five years, and no

amyloidosis was present among those injecting less than two years (40). PWID with AA-amyloidosis in New York had been injecting for significantly longer (mean 16 years) compared to those with focal glomerulosclerosis (mean 10 years), p=0.05, and were significantly older (mean 40 and 32 years, p=0.025) (10). Similarly, PWID diagnosed with renal AA-amyloidosis in Frankfurt, Germany had been injecting longer, 14-27 years (median 20.5) when compared to those with other renal diseases, 7-19 years (median 12.5), p=0.056 (8).

Co-infections

Coinfection data was reported in 19 of the 37 studies. Prevalence of blood borne viruses (BBV) was high among the 177 PWID with AA-amyloidosis, with 82 HCV positive (46%); 28 with HIV/AIDS (15.8%); and 30 with hepatitis B (16.9%). Six had tuberculosis (3.4%) (Table 2). In the German study, 67% (8/12) of those with AA-amyloidosis had HIV, compared with 17% (2/12) of those with another renal diagnosis (p=0.036) (8).

Clinical outcomes

Morbidity and mortality

PWID diagnosed with AA-amyloidosis generally displayed symptoms of nephrotic syndrome (proteinuria, oedema). Their typical trajectory following diagnosis was rapid deterioration of renal function requiring haemodialysis, leading to end-stage renal failure, and eventually death (4, 8, 9, 11, 17, 21, 27, 30, 33, 38). Mortality was high; of the 147 PWID diagnosed with AA-amyloidosis, 45 (31%) died in follow-on hospital care (Table 2) (8, 9, 11, 16, 17, 21, 27, 30, 36). Thirty-nine PWID (22%) were first diagnosed at post-mortem (29, 33, 39, 40). Ten studies reported death among PWID soon after diagnosis or admission to hospital (8, 9, 11, 16-18, 21, 27, 30, 36) (Appendix 3). In the San Francisco study where 24 PWID were diagnosed with AA-amyloidosis subsequent to renal biopsy, 15 (75%) commenced dialysis. Of the 15, 13 (87%) died within six years of biopsy (73% within the first three years) and two were confirmed alive at date of study publication (18). Among the five who did not start dialysis, three were lost to follow-up, with two confirmed alive three years later. In the UK,

median survival after an AA-amyloidosis diagnosis was significantly shorter among PWID (25 months), compared to other AA-amyloidosis patients on dialysis (52 months) (11).

Among all included studies: 71 PWID were documented with end-stage renal failure, 58 commenced dialysis, 15 deaths were reported from sepsis (8, 11, 18, 21), six were lost to follow-up (7, 18, 22, 25), and 16 stopped injecting (7, 8, 11, 16-18, 21, 23) (Appendix 3). For the majority, the primary organ impacted by AA-amyloidosis was the kidneys. Other organs reported with amyloid deposits were: adrenal gland; liver; gut; lung; thyroid; parathyroid; and spleen. Time of progression from diagnosis to end-stage renal failure ranged from two weeks (30) to six years (17).

Positive treatment outcomes

Positive outcomes were reported among 19 PWID with AA-amyloidosis (Appendix 3) (6-9, 11, 17, 18, 20, 23, 31, 34, 35, 41, 43). These included: disappearance/reduction of proteinuria, oedema and nephrotic syndrome; improvement or stabilisation in renal function so that dialysis was no longer required; and disappearance of amyloidosis. Positive clinical improvements in PWID with AA-amyloidosis were associated with injecting cessation, antibiotic treatment for SSTI and resolution of chronic inflammation. Ten PWID who showed a substantial improvement in renal function all reported injecting cessation (7, 8, 11, 17, 18, 23).

Successful treatment of the underlying infection and resolution of any accompanying inflammation is associated with positive AA-amyloidosis outcomes (4, 7, 16, 35, 43). Reducing amyloid deposits in the body is crucial to survival; death was 17.7 times more likely among patients with higher (≥ 155 mg/liter) SAA concentrations in the body compared to less than <4 mg/liter (4). Evidence of reductions in amyloid load or deposits were demonstrated in four studies in which: patients were treated with antibiotics (4, 6, 31), received treatment for the underlying inflammatory disease or SSTI (4, 31), or ceased injecting (4, 11). The use of diuretics (20), oral colchicine (34), and low-salt high-protein diet (20), were reported as beneficial in proteinuria resolution.

Screening interventions

From 1978, study authors consistently recommend that clinicians add amyloidosis to the list of nephropathies experienced by PWID, and prioritise diagnostic investigations amongst those who: have a long injecting history; inject subcutaneously; have proteinuria, renal impairment or HIV (9, 11, 17, 20, 21, 26, 28, 32, 33, 37, 38, 42). Study authors suggest implementation of AA-amyloidosis risk screening among PWID through urinalysis (11), with the potential addition of bone scans (25) (to evaluate the extent of the disease), C-reactive protein tests (to screen for chronic inflammation) (11), and electron microscopy (20, 24).

Challenges to treatment

Treatment of AA-amyloidosis or improvements in renal function were negatively influenced by: failures in diagnosis or referral (8, 9, 11); rapid deterioration of renal function (16, 18, 35); challenges in starting or adhering to dialysis due to severely damaged or occluded veins; and continued injecting (9, 11, 17, 27, 44). Loss to follow-up (4, 7, 8, 11, 18, 22, 31) and development of other complications were also commonly reported (17) (Appendix 3).

DISCUSSION

Our review is the first to systematically analyse the evidence for AA-amyloidosis among PWID. The omission of AA-amyloidosis from a recent review of injecting related injuries and diseases among PWID (1) highlights lack of awareness. With improved awareness, preventative action can be taken and fatalities avoided. We fill an important gap in the literature for an overlooked, rare, but potentially devastating condition. Of the 64 full text articles reviewed, none were published in journals focused on drug use, addiction or dependence, or aimed at practitioners in these fields. However, the majority of the existing literature was found to be of good quality.

The current evidence base for AA-amyloidosis among PWID spans back over four decades, yet epidemiological data are weak (studies generally underpowered) and case reports predominate.

Most studies report on PWID with advanced disease, or at post-mortem. Sample sizes are small and studies are geographically limited or restricted to a single ethnic group. It is hard, therefore, to ascertain a full picture of the disease burden of, or clinical outcomes for PWID with, AA-amyloidosis. Despite some suggestion of increased disease burden over time, most data are before 2000 and lack generalisability to current PWID populations. Older studies are unlikely to reflect current patterns of injecting drug use; new psychoactive substances, for example, are associated with increased frequency of injection and SSTI risk (49).

There are no reports on interventions to prevent AA-amyloidosis among PWID and the evidence on treatment adherence is weak. Consistent, however, are strong recommendations for AA-amyloidosis risk screening among PWID and referral for confirmatory investigations. Proteinuria is a common symptom of AA-amyloidosis and other kidney diseases (50) and there are simple, inexpensive yet non-specific tests that can be used to detect this (21). Implementing screening could help detect signs of renal impairment and initiate strategies to facilitate remission of the nephrotic syndrome, avert renal failure, and reduce amyloid deposits as early as possible. Confirmatory tests such as SAA scan and renal biopsy are required to ascertain diagnosis and initiate treatment (11). Despite the potentially positive benefit of early intervention, we found no evidence of AA-amyloidosis risk screening implementation among PWID.

These recommendations are made in light of strong evidence of good outcomes among those detected early, and those who receive treatment to resolve the underlying inflammation (7, 11, 22, 23, 35). Mortality is associated with late diagnosis (8, 9, 11), loss to follow-up (4, 7, 8, 11, 18, 22, 31), continued injecting (9, 11, 17, 44), and difficulties adhering to dialysis (11, 27, 44). Missed diagnoses are evident; 22% (n=39) of all cases were identified at post-mortem. Given that the symptoms of AA-amyloidosis, like other kidney diseases, are subtle and likely to mimic general ill health among PWID, missed diagnosis may be prevalent. End-stage AA-amyloidosis related renal failure can result in a cardiac arrest; with deaths incorrectly attributed to heart conditions (51).

Our review finds strong evidence of an association between SSTI and AA-amyloidosis. Among PWID, injecting-related SSTIs are a significant cause of morbidity and premature mortality (1, 52-54) and there is evidence of increasing SSTI prevalence (53, 54). Timely access to healthcare among PWID is generally suboptimal – exacerbating chronicity (53-55). In the UK, for example, up to 60% (~120,000) of PWID report recent SSTIs, with 10% reporting SSTI-related hospital admissions per year (11, 56, 57). The majority of these hospitalisations are avoidable, reflecting delays in primary care access (4, 57, 58). Given the current burden of SSTI among PWID, it is imperative not only that AA-amyloidosis risk be considered among PWID with chronic SSTI, but that priority is given to the development of innovative, accessible, and acceptable SSTI prevention and care interventions.

Similarly, untreated HIV leads to a chronic inflammatory state. In addition, HIV might exacerbate chronic infection susceptibility and severity, enhancing AA-amyloidosis risk (8, 11, 21). Sub-clinical liver disease, associated with HCV, may also contribute to reduced clearance of SAA protein leading to accumulation of SAA in the kidneys (18). High co-infection presence may be attributable to the common risks for BBV and SSTIs among this population (18).

Injecting cessation is recommended to enable positive outcomes among those diagnosed. It is posited that drug injecting can exacerbate inflammation, particularly when related to SSTIs (11). There is, however, no literature contextualising AA-amyloidosis within a harm reduction paradigm. It is unclear whether it is the act of injecting *per se* that exacerbates inflammation (and poor AA-amyloidosis outcomes), or the injecting risk environment which potentiates harm. Poor injection hygiene, subcutaneous injecting and drug quality are associated with SSTI (53, 54).

SSTI causation is incompletely understood. Chronic inflammation, due to ongoing and/or untreated abscesses, ulcers, and other SSTIs, potentiates AA-amyloidosis risk. Loss of venous access – due to multiple mechanisms, including type of drug, acidification of drug for solubilisation and acidic drug solution – is critical in the causal pathway to increased sub-cutaneous injection (59). Increased sub-cutaneous injection in turn leads to increased risk for SSTI and chronic SSTI (47, 60). The acidity and

impurity of 'black tar heroin', generally used in the western US, exemplifies the risk. Black tar heroin users have a substantially higher prevalence of SSTI than do users of powder heroin on the East Coast – illustrating the geographic variation in chronic SSTI and associated sequelae, including AA-amyloidosis (60).

It is impossible to ascertain from the literature if modifications to the risk environment – such as provision of pharmaceutical heroin and/or sterile injecting equipment – would achieve outcomes comparable with injection cessation. In the absence of such widespread interventions, there is a need to reinvigorate supports for injecting route transitions and SSTI prevention in collaboration with the affected community.

Limitations

Our review is subject to selection bias as the baseline characteristics of the study populations likely differ in several key respects, for example in relation to geographic distribution of brown and black tar heroin and associated SSTI risk. Further, studies which did not report AA-amyloidosis would not be included in our review; explicit reference to AA-amyloidosis was required by our search strategy. It is not generally the case that AA-amyloidosis can be observed grossly and without Congo Red histological tissue stain. Therefore, routine hospital post-mortem may not identify AA-amyloidosis even if it is both present and clinically important. Given this, we hesitate to assume that surveys of PWID (particularly retrospective post-mortem studies) would necessarily identify AA-amyloidosis were AA-amyloidosis not already being considered. Due to the high level of heterogeneity between studies in which the proportion of PWID with AA-amyloidosis was estimated, a meta-analysis was only possible on three post-mortem studies. Finally, a significant proportion of the identified studies were unavailable (n=10) for full text review. This has had the effect of biasing our review in favour of more recent published studies.

In short, we do not seek to suggest a global prevalence of AA-amyloidosis, only a range of prevalence estimates in at-risk populations.

CONCLUSION

This is the first systematic review assessing the literature on AA-amyloidosis among PWID. We synthesised 37 studies, together representing 817 PWID. Of the 177 (22%) PWID with AA-amyloidosis, 157 (89%) had SSTIs. Limitations in the literature make it difficult to estimate AA-amyloidosis prevalence among PWID, or if the recommended urinalysis screening is warranted. Given high mortality among diagnosed PWID, formative research is required. Early intervention might ameliorate progression to end stage renal failure and associated difficulties with dialysis adherence. Innovations for SSTI prevention and care are crucial regardless of AA-amyloidosis burden; SSTIs alone cause considerable suffering among PWID and account for high ambulatory care uptake. Awareness of AA-amyloidosis is low among harm reduction and addiction practitioners and researchers; also among communities of PWID – it is crucial that those most at risk are involved in any intervention development.

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Figure 1. PRISMA Flow Chart

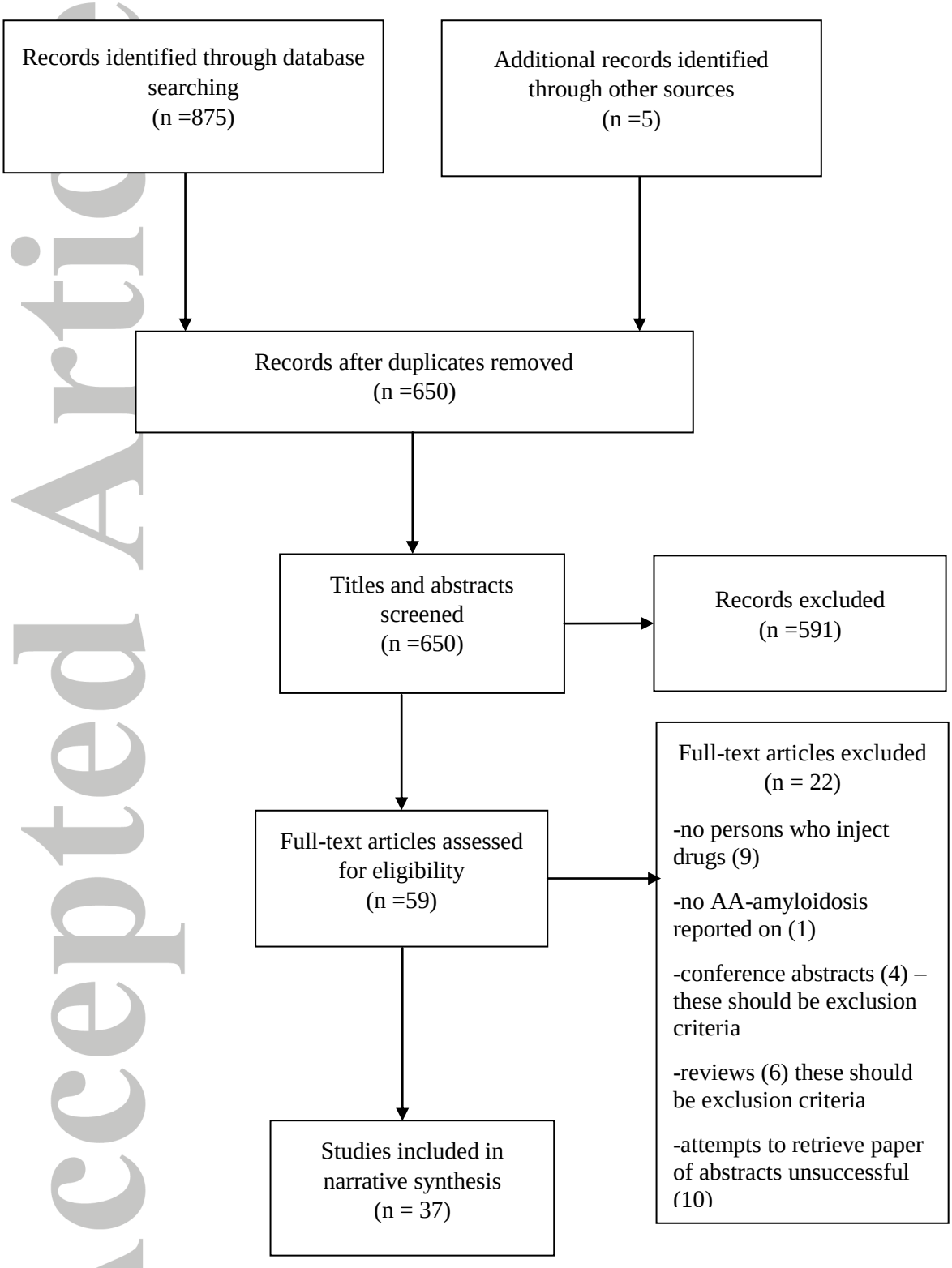

Table 1. Included studies by location, year of publication, type of report, and type of journal

	No. of studies N=37	Study references
Country/Cities		
USA: New York (14); Los Angeles (2); San Francisco (2); Chicago (1), Maryland (1); Texas (1); Kansas City (1; Massachusetts (1); Yale (1)	24	(6, 10, 16-18, 20-38)
UK: London	6	(4, 11, 21, 41-44)
Germany: Frankfurt; Main	2	(8, 39)
Portugal: Porto	1	(19)
Spain: Barcelona	1	(7)
Norway: Oslo	1	(9)
Serbia: Niš	1	(40)
India: New Delhi	1	(45)
Year of publication		
2010-2015	7	(8, 18, 22, 36, 38-40)
2000-2009	9	(4, 9, 11, 19, 21, 41, 42, 44, 45)
1990-1999	5	(33-35, 37, 43)
1980-1989	9	(7, 10, 16, 23, 25, 27, 29-31)
1970-1980	7	(6, 17, 20, 24, 26, 28, 32)
Type of report		
Case report	24	(6, 7, 20-28, 30-32, 34-38, 41-45)
Case series	3	(9, 16, 17)
Post-mortem review	4	(29, 33, 39, 40)
Cohort study/ biopsy-review	5	(4, 8, 11, 18, 19)
Cross-sectional study	1	(10)
Journal type		
Medical/Pathology	21	(4, 6, 11, 16, 17, 20, 21, 24-32, 35-37, 40, 41, 45)
Nephrology	13	(7-10, 18, 19, 22, 23, 34, 38, 39, 43, 44)
Hepatology	1	(33)
STD/AIDS	1	(42)

Table 2 Summary of the demographic characteristics, and clinical outcomes of the 781 people who inject drugs (PWID) from 37 included studies

			Gender of PWID: n (%)			Comorbidities among PWID diagnosed with AAA n (%)						Outcomes after PWID diagnosed with AAA: n (%)				
Report type	**No. of studies**	**Total No. of PWID reported on**	**Males**	**Females**	**NR**	**AAA**	**SSTI**	**HEP C**	**HEP B**	**HIV/ AIDS**	**TB**	**Death on follow-up**	**Required dialysis**	**Condition Improved**	**Loss to follow-up**	**Stopped injecting**
Case series and case reports	27	**59**	45 (76.3)	14 (23.7)	0 (0.0)	**59 (100.0)**	58 (98.3)	17 (28.8)	13 (22.0)	7 (11.9)	3 (5.1)	18 (30.5)	15 (25.4)	11 (18.6)	3 (5.1)	8 (13.6)**
Cohort studies/review of renal biopsies	5	**100**	63 (63.0)	24 (24.0)	13 (13.0)	**70 (70.0)**	56 (80.0)	65 (92.8)	17 (24.3)	14 (20.0)	3 (4.3)	27 (38.6)	33 (47.1)	8 (11.4)	3 (4.3)	8 (11.4)
Post-mortem reviews	4	**587**	51 (8.7)	5 (0.9)	531 (90.5)	**34 (5.8)**	30 (88.2)	NR	NR	7 (20.6)	NR	NA	NA*	NA	NA	NA
Cross-sectional study	1	**35**	NR	NR	35 (100.0)	**14 (40.0)**	13 (92.9)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total	**37**	**781**	**159 (20.4)**	**43 (5.5)**	**579 (74.1)**	**177 (22.7)**	**157 (88.7)**	**82 (46.3)**	**30 (16.9)**	**28 (15.8)**	**6 (3.4)**	**45 (25.4)**	**48 (27.1)**	**19 (10.7)**	**6 (3.4)**	**16 (9.0)**

'AAA'- refers to AA-amyloidosis; 'NR'- not reported; 'NA'- not applicable; *- 10 reported to have required dialysis before death; **-includes one which reported reduced frequency of injecting; 'SSTI'- skin and soft tissue infections; 'HEP C'- Hepatitis C; 'HEP B'- Hepatitis B; 'TB'-tuberculosis;

Table 3. Reports which determined proportion of PWID with AA-amyloidosis at post-mortem or post-biopsy.

Study reference and type of study,	Period of data collection	Study location	Sample size of PWID	Proportion of PWID with AAA %
Post-mortems				
(39) Post-mortem study	1 January 2009 to 30 April 2011	Germany, Frankfurt/ Main	105	1.9
(33) Post-mortem study	1981 to 1990	USA, New York	292	4.1
(29), Post-mortem study	1 October 1981 to 4 December 1981, and February 1982	USA, New York	150	4.7
(40) Post-mortem study	not stated	Serbia	40	22.5
Live diagnoses (after renal biopsy)				
(10) Cross-sectional study	1977 to 1980	USA, New York	14	29
	1981-1983	USA, New York	21	48
(19) Cohort study	January 1993 to December 2001	Portugal	19	5.26
(8) Cohort study	1 April 2002 to 31 March 2012	Germany	24	50