Original Article

A Comparative Analysis Between Antibiotic- and Nonantibiotic-Associated Delayed Cutaneous Adverse Drug Reactions

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What is already known about this topic? Cutaneous adverse drug reactions (cADR) are associated with significant morbidity and mortality. Antimicrobials are thought to be the commonest cause.

What does this article add to our knowledge? Antibiotics made up almost 50% of cADR cases, glycopeptides (vancomycin and teicoplanin), sulfonamides, and beta-lactams predominating. Variations in clinical presentation, number of implicated antibiotics, and outcomes were noted in patients with antibiotic-associated versus nonantibiotic-associated cADR.

How does this study impact current management guidelines? Clinicians should have a heightened awareness of antibiotic-associated cADR. The development of tools to aid causality assessments is required because of the higher number of implicated antibiotics in antibiotic-associated cADR and inferior patient outcomes.

BACKGROUND: The difference in clinical presentation, causality assessments, and outcomes of patients with delayed antibiotic-associated cutaneous adverse drug reactions (AA-cADR) and nonantibiotic-associated (NA)-cADR is ill defined.
OBJECTIVE: We examined the etiology of AA-cADR, with regard to the type of antibiotic exposure, allergy labeling, and patient outcomes, in comparison with NA-cADR.
METHODS: A retrospective observational inpatient cohort study of cADR was performed from January 2004 to August 2014. Patients were divided into AA-cADR and NA-cADR groups for analysis. cADR was defined as erythema multiforme, fixed drug eruption, acute generalized erythematous pustulosis, drug reaction with eosinophilia and systemic symptoms (DRESS), drug-associated linear IgA disease, Stevens-Johnson syndrome, and toxic epidermal necrolysis.
RESULTS: Of the 84 patients with cADR, 48% were AA-cADR. Male sex (60% vs 32%, $P = .004$), median length of stay (14.5 vs 11 days, $P = .05$), median Charlson comorbidity index (3 vs 1, $P = .03$), and inpatient mortality (20% vs 5%, $P = .04$) were higher in AA-cADR compared with NA-cADR. The median drug latency was lower in AA-cADR (6 vs 20 days, $P = .001$). Sulfonamide antibiotics and glycopeptides were implicated in 20% of AA-cADR. DRESS was more frequently reported in AA-cADR. After cADR diagnosis, further antibiotic therapy was administered in 64% of patients, higher in AA-cADR (75%, 30 of 40) compared with NA-cADR (55%, 24 of 44) ($P = .06$). Fluoroquinolones (53% vs 21%, $P = .02$), glycopeptides (vancomycin and teicoplanin; 70% vs 38%, $P = .05$), and carbapenems (33% vs 13%, $P = .11$) were used more commonly in AA-cADR.
CONCLUSIONS: Antibiotics were the cause of cADR requiring hospital admission in 48% of episodes, and were associated with longer length of stay, higher age-adjusted Charlson comorbidity index, shorter drug latency, and mortality. In AA-cADR, glycopeptide and sulfonamide antibiotic exposure predominated. **(J Allergy Clin Immunol Pract 2016;4:1187-93)**

Key words: *Allergy; Drug reactions; Steven-Johnson syndrome; Toxic epidermal necrolysis*

Delayed cutaneous adverse drug reactions (cADR) represent a range of disorders initiated by idiosyncratic T-cell-mediated immune responses. Severe cutaneous adverse reactions

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Abbreviations used
AA-cADR- Antibiotic-associated cutaneous adverse drug reactions
AGEP- Acute generalized exanthematous pustulosis
BSA- Body surface area
cADR- Cutaneous adverse drug reaction
DRESS- Drug reaction with eosinophilia and systemic symptoms
EM- Erythema multiforme
FDE- Fixed drug eruption
GN- Gram-negative
IVIG- Intravenous immunoglobulin
LID- Linear IgA disease
MDR- Multidrug resistant
MPE- Maculopapular exanthems
MRSA- Methicillin-resistant Staphylococcus aureus
NA-cADR- Nonantibiotic-associated cutaneous adverse drug reactions
SCAR- Severe cutaneous adverse reaction
SJS- Steven-Johnson syndrome
TEN- Toxic epidermal necrolysis
TMP-SMX- Trimethoprim-sulfamethoxazole
VRE- Vancomycin-resistant Enterococcus faecium

(SCAR)—acute generalized erythematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)—form the extreme end of the spectrum, associated with significant morbidity and mortality.[1,2] Mortality rates for SCAR syndromes have been reported as 12%-54% for SJS, 24% for AGEP, 12%-67% for TEN, 23%-29% for SJS/TEN overlap, and 2%-10% for DRESS.[3,4] However, other commonly encountered inpatient cADR outside of simple maculopapular exanthems (MPE) and urticaria, such as erythema multiforme (EM), fixed drug eruption (FDE), and linear IgA disease (LID), are often excluded in these studies.

Although antimicrobials are a recognized cause of cADR, minimal literature is available in comparing antibiotic-associated (AA)- and nonantibiotic-associated (NA)-cADR. The clinical features, microbiological associations, antibiotic usage, and outcomes of patients with AA-cADR compared with those with NA-cADR are also not well described. The primary objective of our study was to identify the common drug-related causes of inpatient cADR, with a focus on antibiotic precipitants. The secondary objective was to evaluate the differences in clinical presentation, treatment, and outcomes for AA-cADR and NA-cADR. Furthermore, we examined antibiotic prescribing and the rates of multidrug-resistant (MDR) organisms after the diagnosis of AA-cADR, and "antibiotic labeling" after discharge.

METHODS

A retrospective observational cohort study was performed on inpatient cADR at Alfred Health from January 1, 2004, to August 31, 2014, after local ethics committee approval. Alfred Health is an 800-bed tertiary referral center, encompassing statewide (Victoria, Australia) bone marrow transplant, heart/lung transplant, trauma, burns, and HIV services. Patients were identified using International Classification of Diseases (ICD)-10 coding (any inpatient primary or secondary codes: L51.1, L51.2, L27.0, L27.1), Burns unit, Adverse Drug Reaction (ADR) Review Committee, and HIV databases. The Burns unit, ADR Review Committee, and HIV databases are searchable for "phenotype" and maintained by the respective units. Patients were only included once. Patients who were managed exclusively as outpatients were excluded from the analysis. Dermatologists diagnosed all patients with cADR.

Patient baseline demographics (age, sex, country of birth, ethnicity, age-adjusted Charlson comorbidity index) were recorded.[5] cADR history was obtained: type of cADR, histopathological findings, organ involvement, cADR treatment history, and all-cause mortality. The Alfred Health ADR Review Committee assigned a presumed drug causality after cADR diagnosis, which was verified by the Naranjo score (possible, probable, or definite) for all drugs and the algorithm of drug causality assessment (ALDEN) for SJS/TEN syndromes (ALDEN, score $>$ 3).[6,7] The Alfred Health ADR Committee has representatives from pharmacy, infectious diseases, clinical pharmacology, and dermatology present at times of convening. If multiple drugs were implicated, then single drug causality was not assigned. Microbiological culture results (inpatient only) and antibiotic usage (inpatient after cADR diagnosis and after discharge) were recorded. Patients were divided into 2 cohorts: AA-cADR and NA-cADR. The AA-cADR cohort included patients where the primary implicated drug, as assigned by the ADR Committee, had antibacterial or antifungal activity. NA-cADR included all other patients, including those with an unknown precipitant, infective etiology (eg, mycoplasma, cytomegalovirus), or those who received antiretroviral therapy.

Definitions

cADR was defined as EM, FDE, AGEP, DRESS, drug-associated LID, SJS, and TEN. SJS was defined as widespread macules or blisters with skin detachment of $<$10% of body surface area (BSA), TEN if skin detachment was $>$30% BSA, and SJS/TEN overlap with 10%-30% of BSA involvement. DRESS was defined as per regiSCAR criteria.[8] All cases were defined as severe adverse reaction as per WHO definitions.[9,10] For a single implicated drug, the latency period was defined as the period from commencement of the implicated drug to onset of rash. Inpatient onset defined if the primary implicated antibiotic was first administered as an inpatient. Treatment was defined as one or more of surgical debridement, steroid therapy, or intravenous immunoglobulin (IVIG). An immunocompromised host was defined as solid organ transplant recipient, hematological stem-cell transplant recipient, autoimmune/connective tissue disorder, patient with cancer, or recipient of $>$10 mg prednisolone daily for more than 1 month.

Renal involvement was defined as a rise in serum creatinine 50% above upper limit of normal or known patient's baseline. Liver involvement constituted a 2-fold rise in bilirubin, alkaline phosphatase, alanine transaminase, or aspartate aminotransferase values above upper limit of normal.[11] Ocular involvement was defined as conjunctivitis or corneal involvement. Isolation of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), or an MDR gram-negative (GN) organism within 48 hours of cADR diagnosis from clinical specimens was defined as pre-cADR isolation. An MDR GN organism was defined as resistance to at least 2 unrelated classes of antibiotics.[12] Records of patients' antimicrobial allergies were reviewed at discharge and 3 months after discharge (if available). An antibiotic allergy label was defined as a listed antimicrobial agent in the allergy section of the medical record.

Statistical methods

Categorical variables were summarized using count and proportion and compared using a Fisher's exact test. A comparison of

binary variables was made by a 2 × 2 contingency table and Fisher's exact test. Continuous variables were summarized using the median and interquartile range as appropriate and compared using a Wilcoxon rank sum test. Statistical significance was defined as a $P < .05$ (2-tailed) and all statistical analyses were performed using Stata 12.0 (Statacorp, College Station, Tex).

RESULTS

Baseline demographics and types of cADR

During the 10-year investigational period, 84 cases of cADR were identified, of which 48% (40 of 84) were AA-cADR. One hundred and thirty-four drugs were implicated for the 84 cases. TEN was the most frequently reported cADR in both AA-cADR and NA-cADR, with AGEP and DRESS more frequently reported in AA- than NA-cADR (Figure 1). The baseline demographic data shown in Table I demonstrate a male predominance (60%) and a higher median age-adjusted Charlson comorbidity index in AA-cADR. A higher proportion of inpatient onset cADR (30% vs 0%, $P < .001$) and shorter median drug latency (6 days vs 20 days, $P < .001$) were noted in AA-cADR compared with NA-cADR. Fewer AA-cADR cases were biopsy proven when compared with NA-cADR (80% vs 98%, $P = .01$). No difference in baseline immunosuppression (including HIV), prior antimicrobial allergy history, or cADR internal organ involvement was noted between groups ($P > .1$) (Table I). In patients with NA-cADR from an unknown cause, 80% (4 of 5) were SJS or TEN phenotypes, no patients were immunocompromised, only 1 patient required intensive care unit (ICU) admission, and there was no mortality noted.

Implicated antibiotics in AA-cADR

As shown in Table II, the most commonly implicated antibiotic class for AA-cADR was beta-lactams (45%; 28 of 62), with cephalosporins (16%; 10 of 62) being the most frequently reported beta-lactam. Less commonly implicated antibiotics included meropenem, azithromycin, clindamycin, and doxycycline (Table II). Sixty percent (24 of 40) of patients had a beta-lactam antibiotic implicated in AA-cADR, whereas sulfonamide antibiotics and glycopeptides (vancomycin and teicoplanin) were each implicated in 20% (8 of 40) of patients. The examination of antibiotic class and relationship with each type of cADR is outlined in Table III. The median drug latency period was the highest for AA DRESS (11.5 days) and shortest for AGEP (5 days) (Table IV).

Antibiotic usage and microbiological associations in AA-cADR

In total, inpatient antibiotic therapy after cADR diagnosis was used in 64% (54 of 84) patients. This was higher in patients with AA-cADR (75%, 30 of 40) compared with those with NA-cADR (55%, 24 of 44) ($P = .06$), and there was a higher median number of antibiotic classes used in the AA-cADR versus NA-cADR group (3 vs 2, $P = .03$). There was also a higher amount of fluoroquinolones and glycopeptides used in patients with AA-cADR versus NA-cADR (Table III).

Bacteremia was noted in 21% of all patients with cADR; however, there was no statistically significant difference in bacteremia rates between AA-cADR and NA-cADR (25% vs 16%, $P = .15$). Despite a higher number of antibiotics being employed for longer in AA-cADR (Table IV) compared with NA-cADR, there were no significant differences in the individual

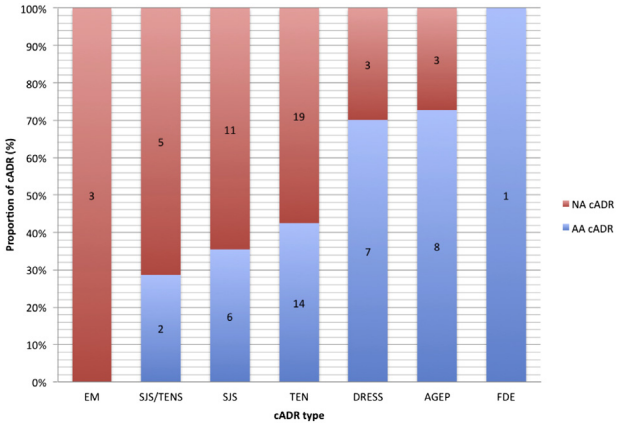

FIGURE 1. Proportion of cADR attributable to antibiotics (AA) and nonantibiotics (NA). *AGEP,* Acute generalized erythematous pustulosis; *cADR,* cutaneous adverse drug reactions; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *EM,* erythema multiforme; *FDE,* fixed drug eruption; *SJS,* Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis. Note: Numerals within columns refer to the number of patients not implicated antimicrobials.

rates of MRSA, VRE, or MDR GN acquisition or infection between AA-cADR and NA-cADR after diagnosis (data not shown). As a composite endpoint, however, there was a higher rate of MDR organism (MRSA, VRE, and MDR GN) acquisition in the AA-cADR group compared with the NA-cADR group (35% vs 14%, respectively, $P = .04$).

Treatment

Eighty-five percent of the cohort received treatment with at least one of systemic steroids, IVIG, or surgical debridement (Table II). A higher proportion of NA-cADR received some form of treatment (93% vs 75%, $P = .02$) with systemic steroid therapy being the most commonly employed (53%). IVIG was used in more patients with AA-cADR than NA-cADR (70% vs 29%, $P = .07$). Overall, patient mortality from cADR was 12%, with the mortality from AA-cADR being significantly higher than that of NA-cADR (20% vs 5%, respectively, $P = .04$) (Table III). The 60-day all-cause mortality was notably the highest for TEN (36%, 5 of 14), whereas no deaths occurred in the DRESS, FDE, or LID groups (Table IV). In patients with SCAR (excluding FDE, EM, LID), the inpatient mortality was 12% (10 of 84), higher in AA versus NA (80%, 8 of 10 vs 20%, 2 of 10, $P = .02$).

Allergy labeling in cADR

In patients with AA-cADR, 20% (8 of 40) were rechallenged with an antibiotic from the same class during the inpatient admission. An adverse reaction was noted in only 1 case, which was an isolated eosinophilia in a patient who received piperacillin-tazobactam after flucloxacillin-induced SJS. Sixty-three percent (5 of 8) of patients with a beta-lactam AA-cADR received at least 1 beta-lactam antimicrobial during the index admission, carbapenem in all cases, without ADR. No cephalosporins were used in these patients. In patients with AA-cADR, all patients who survived to discharge (n = 32) were subsequently prescribed at least 1 implicated antibiotic in the

TABLE I. Baseline demographics for cohort, comparing AA versus NA-cADR

Patient characteristic	AA-SCAR, no. (%) n = 40	NA-SCAR, no. (%) n = 44	Total, no. (%) n = 84	*P* value
Age				
Median (IQR)	57 (48, 68)	50 (32, 66)	54 (37, 67)	.06
Sex				
Male	24 (60)	14 (32)	38 (45)	.004
Prior allergies	22 (55)	16 (36)	38 (45)	.12
Prior antibiotic allergies	17 (43)	12 (27)	29 (35)	.17
Age-adjusted Charlson comorbidity index				
Median (IQR)	3 (1, 6)	1 (0, 3.5)	2 (0, 4.5)	.03
Season of diagnosis				
Summer	12 (30)	9 (21)	21 (25)	
Autumn	6 (15)	18 (41)	24 (29)	.21
Winter	13 (32)	11 (25)	24 (29)	
Spring	9 (23)	6 (14)	15 (18)	
Intensive care unit admission after cADR	19 (48)	15 (34)	34 (40)	.27
Immunosuppressed	11 (28)	12 (27)	23 (27)	1
HIV infected	3 (7.5)	3 (6.8)	6	1
Inpatient onset	12 (30)	0	12 (14)	.001
Drug latency*				
Median (IQR), d	6 (5.4, 10.4)	20 (16.4, 31)	12 (8, 23)	.001
Single implicated drug	26 (65)	37 (85)	63 (75)	.07
Biopsy proven	32 (80)	43 (98)	75 (89)	.01
Internal organ involvement				
Liver	18 (45)	26 (59)	44 (52)	.14
Renal	3 (9)	2 (5)	5 (7)	
Ocular	2 (6)	1 (2)	3 (4)	
Gastrointestinal	11 (34)	19 (44)	30 (36)	
	2 (6)	1 (2)	3 (11)	
More than 1 organ involved	3 (9)	6 (14)	9 (10)	.48

AA-cADR, Antibiotic-associated cADR; *cADR,* cutaneous adverse drug reactions; *IQR,* interquartile range; *NA-cADR,* nonantibiotic-associated cADR; *SCAR,* severe cutaneous adverse reaction.
*Latency estimated only in cases where a single drug was implicated (n = 63).

medical record. Despite an inpatient cADR episode and documentation on discharge, 16% (5 of 33) had no antibiotic allergy label listed at the 3-month follow-up. Twenty-five percent (8 of 32) of patients with AA-cADR had recorded antibiotic prescriptions after discharge from hospital, 38% (3 of 8) of which were moxifloxacin. In the 4 patients with AA-cADR related to a beta-lactam who received an antibiotic after discharge, a beta-lactam was prescribed in 50% without reported adverse effects. No patients received the same offending antibiotic after discharge.

DISCUSSION

Previous reports of inpatient cADR have primarily focused on SCAR from NA causes, including antiepileptics, antiretroviral, and anti-inflammatories.[2,3,13-15] This is despite antibiotics being more commonly implicated and associated with both significant mortality and morbidity.[16] A dedicated comparative analysis of AA-cADR versus NA-cADR has not been previously undertaken. We report on a 10-year history of inpatient severe cADR, excluding isolated MPE, from an Australian tertiary referral center with a mixed patient population, and compare causes, cADR subtypes, and patient outcomes between AA- and NA-cADR.

Overall, the majority of inpatient cADR episodes represented SCAR phenotypes, whereas EM, FDE, and LID were infrequently encountered. We demonstrated that almost 50% of cADR was AA. This is similar to other centers that have previously reported antibiotics to be a common cause of SCAR.[3] Our center recognized beta-lactams as the most frequently associated antibiotic class, which may be due to a higher overall frequency of prescribing of this antibiotic class. The most commonly reported individual antibiotics causing AA-cADR were trimethoprim-sulfamethoxazole (TMP-SMX) and vancomycin. This contrasts to previous reports, where penicillin was the primary causative antibiotic for SCAR and TMP-SMX/cephalosporins for cADR.[16,17] For DRESS, sulfonamide antibiotics, vancomycin, and minocycline have been commonly reported, similar to our findings.[2,13]

When comparing baseline characteristics between AA-cADR and NA-cADR, we identified a higher male predominance, inpatient onset, and medical complexity in the AA-cADR group. There was no difference in ICU admission rate, length of stay, or treatment between the 2 groups. Notwithstanding this, a higher rate of 60-day all-cause mortality was noted in the AA-cADR group compared with NA-cADR (20% vs 5%). This was despite higher rates of SJS/TEN in NA-cADR, which are typically associated with higher mortality.[1] Concurrent inpatient stay

TABLE II. Implicated antibiotics in the AA-cADR cohort

Antibacterial	No. (%) n = 62
Beta-lactams	28 (45.2)
Penicillins	2 (3.2)
Penicillin V/G	2
Aminopenicillins	7 (11.3)
Amoxycillin/Amoxycillin-clavulanate	6
Ampicillin	1
Antistaphylococcal penicillins	8 (12.9)
Flucloxacillin	3
Piperacillin-tazobactam	4
Ticarcillin-clavulanate	1
Cephalosporins	10 (16.1)
Cephalexin	2
Cefazolin	2
Cefuroxime	1
Ceftriaxone	3
Cefepime	2
Carbapenem	1 (1.6)
Meropenem	1
Glycopeptides	8 (12.9)
Vancomycin	7
Teicoplanin	1
Sulfonamide antimicrobials	8 (12.9)
Macrolides	3 (4.8)
Erythromycin	2
Azithromycin	1
Quinolones	3 (4.8)
Ciprofloxacin	3
Azoles	3 (4.8)
Fluconazole	3
Lincosamides	2 (3.2)
Lincomycin	1
Clindamycin	1
Nitroimidazoles	2 (3.2)
Metronidazole	2
Other	
Daptomycin	1 (1.6)
Roxithromycin	1 (1.6)
Doxycycline	1 (1.6)
Pentamidine	1 (1.6)
Liposomal amphotericin B	1 (1.6)

AA-cADR, Antibiotic-associated cutaneous adverse drug reactions.

and higher medical comorbidities are potential causes for the increased mortality; however, a varied pathophysiology in AA-cADR is also possible. Our overall mortality rate (12%) was lower than in the regiSCAR study by Sekula et al. When cases of EM, LID, and FDE are excluded, overall SCAR mortality for the cohort remains at 12.8% (10 of 78), still higher for AA than NA patients. Nonetheless, our AA-cADR mortality (20%) was remarkably similar to that reported previously (21.6%).[4,13,16] Our mortality rate of 5% in the NA-cADR group (2% in NA-SCAR) was similar to an antiepileptic-associated SCAR study (6.49%).[16] The 0% mortality rate seen in our AA DRESS was lower than the 12% reported from the Taiwanese antibiotic SCAR population.[1,16]

It has been noted previously that most cases of T-cell-mediated hypersensitivity overall occur within 8 weeks of drug commencement (85%-100%), with no clear risk identified beyond 8 weeks.[13] In fact, a delay of 4-28 days is most indicative.[13] We noted a large disparity in latency period between AA-cADR and NA-cADR (6 days vs 20 days). This may be in part be secondary to the higher rate of inpatient onset noted in AA-cADR, leading to earlier detection and cessation of the implicated drug. Nonetheless, this difference may help inform clinical practice when assigning drug causality, especially in patients on multiple antibiotics or drugs associated with SCAR syndromes. For AA-cADR specifically, the latency period also varied for individual syndrome, highest with DRESS and lowest for AGEP. This exact timing for DRESS and AGEP was replicated in the study by Lin et al for antibiotic SCAR.[16] An even longer median latency was reported for DRESS in the regiSCAR prospective cohort (22 days).[2]

Although the indications for antimicrobial use may be different between AA- and NA-cADR, the implications of restricted antibiotic use to the patient and hospital are significant. The need for antibiotics in AA-cADR was highlighted by the greater bacteremia rate and trend toward increased MDR GN acquisition. The higher use of glycopeptides (vancomcyin and teicoplanin) and quinolones, and increased median number of antibiotic classes employed in the AA-cADR group, is likely the result of confusion surrounding antibiotic prescribing in this setting. This contrasts against the prescribing data in Alfred Health inpatients without antibiotic allergy "labels," which largely consists of beta-lactam antibiotics: cephazolin, ceftriaxone, and piperacillin-tazobactam.[18]

A high number (20%) of patients with AA-cADR were also noted to be challenged with antibiotics of a similar class. Interestingly, 63% (5 of 8) of patients with a beta-lactam AA-cADR were rechallenged with meropenem during the acute episode, without an adverse event. The low rate of ADR considering this rechallenge history has implications for either the initial causality assessment or dogma around antibiotic cross-reactivity in T-cell-mediated reactions, especially the safety of carbapenem use in other beta-lactam-related cADR.[19,20]

Further complicating antibiotic choice is the higher rate of multiple implicated drugs in AA-cADR. Therefore, the ability to assign drug causality, especially in cases of AA-cADR where multiple agents and/or classes are involved is paramount. Although the sensitivity of *in vivo* skin testing, in particular patch testing, for some SCAR syndromes is poor (approximately 20% for SJS/TEN), it can be up to 80% for others such as DRESS.[21,22] Future validation of *ex vivo* T-cell enzyme-linked immunospot assays, which have primarily been explored in antiretroviral hypersensitivity,[23,24] may allow assignment of drug causality whilst avoiding *in vivo* testing, which is both contraindicated and potentially unhelpful in acute SJS/TEN/DRESS.[23-26] Multidisciplinary approaches that include detailed clinical appraisal, ADR Committee review, utilization of SJS/TEN scoring systems (eg, ALDEN), *in vivo* skin testing, and *ex vivo* assays are required to ensure accurate causality assessments.

The limitations of this study include its retrospective nature, small sample size, presence of potential confounders between groups including imbalance of cADR types, absence of follow-up allergy testing, and reliance on ICD-10 coding for case capture.

TABLE III. Treatment, antibiotic usage, and outcomes for AA-cADR and NA-cADR

Outcome	AA-cADR, no. (%) n = 40	NA-cADR, no. (%) n = 44	Total, no. (%) n = 84	*P* value
Treatment	30 (75)	41 (93)	71 (85)	.02
Treatment type (n = 30)				
Steroid*	13 (43)	25 (61)	38 (53)	.16
IVIG	21 (70)	12 (29)	33 (46)	.07
IVIG and steroid	4 (13)	7 (17)	11 (16)	.5
Debridement	3 (10)	7 (17)	10 (14)	.74
Median number antibiotic classes employed†	3 (IQR 2-5)	2 (IQR 1.25-2.75)	2 (IQR 2-4)	.03
Median antibiotic duration, d	14.5 (IQR 8-42)	11.5 (IQR 7-24.5)	12.5 (IQR 8-31)	.23
Median antibiotic duration, d/Length of stay, d	0.915 (IQR 0.48-1.5)	0.69 (IQR 0.47-1.23)	0.87 (IQR 0.47-1.33)	.23
Patients received antibiotics after cADR	30 (75)	24 (55)	54 (64)	.06
Beta-lactams	20 (67)	22 (92)	42 (77)	.05
Penicillins‡	12 (40)	13 (54)	25 (54)	.05
Cephalosporins	10 (33)	11 (46)	21 (39)	.4
Carbapenems	10 (33)	3 (13)	13 (24)	.11
Monobactams	3 (10)	1 (4)	4 (7)	.62
Fluoroquinolones	16 (53)	5 (21)	21 (39)	.02
Aminoglycosides	7 (23)	7 (29)	14 (26)	1
Glycopeptides	21 (70)	9 (38)	30 (56)	.05
Inpatient all-cause mortality	8 (20)	2 (5)	10 (12)	.03
60-d attributable mortality	4 (10)	1 (1)	5 (6)	.19
60-d all-cause mortality§	8 (20)	2 (5)	10 (12)	.04
Infective cause	3 (8)	0	3 (4)	.24

AA-cADR, Antibiotic-associated cADR; *cADR,* cutaneous adverse drug reactions; *IQR,* interquartile range; *IVIG,* intravenous immunoglobulin; *NA-cADR,* nonantibiotic-associated cADR.
*Steroid therapy included prednisolone, hydrocortisone, or dexamethasone therapy in a patient not usually on therapy or a 50% increase in dose in those previously taken.
†Inpatient prescribing after diagnosis of cADR.
‡Penicillins: penicillin V, penicillin G, aminopenicillins, and antistaphylococcal penicillins.
§Infective causes were infective endocarditis with septic emboli, enterococcus urosepsis, and staphylococcal bacteremia.

TABLE IV. The etiology and patient characteristics of AA-cADR

	Phenotypes, no. (%)						
Patient characteristics	Linear IgA n = 2	AGEP n = 8	FDE n = 1	DRESS n = 7	SJS n = 6	SJS/TEN n = 2	TEN n = 14
Associated antibiotics							
Penicillins*	–	1 (13)	–	1 (14)	2 (33)	–	3 (21)
Cephalosporins	–	–	1 (100)	–	–	–	1 (7)
Fluoroquinolones	–	–	–	–	1 (17)	–	–
Glycopeptides	2 (100)	1 (13)	–	2 (29)	–	–	–
Sulfur antimicrobials	–	–	–	1 (14)	3 (50)	1 (50)	3 (21)
Erythromycin	–	1 (13)	–	–	–	–	1 (7)
Fluconazole	–	–	–	–	–	1 (50)	–
Multiple drugs	–	5 (63)†	–	3 (43)‡	–	–	6 (43)§
Age (median)	69.5	63.5		57	43	42	48
Sex (male)	2 (100)	4 (50)	0	5 (71)	4 (67)	1 (50)	8 (57)
Age-adjusted Charlson comorbidity index (median)	4	3		6	4	4	3
Latent period (median, d)	8.5	5		11.5	5		8
Length of stay (median, d)	20	14	9	16	12.5	10.5	16
Mortality (60-d all-cause)	0	1 (13)	0	0	1 (17)	1 (50)	5 (36)

AA-cADR, Antibiotic-associated cutaneous adverse drug reactions; *AGEP,* Acute generalized erythematous pustulosis; *DRESS,* drug reaction with eosinophilia and systemic symptoms; *FDE,* fixed drug eruption; *SJS,* Stevens-Johnson syndrome; *TEN,* toxic epidermal necrolysis.
*Penicillins including penicillin V/G, aminopenicillins, and antistaphylococcal penicillins.
†Amoxycillin clavulanate, doxycycline, ceftriaxone, metronidazole, timentin, flucloxacillin, ceftriaxone, fluconazole.
‡Cefazolin, teicoplanin, vancomycin, tazocin, clindamycin, daptomycin.
§Ciprofloxacin, amoxycillin clavulanate, fluconazole, ceftriaxone, roxithromycin, lincomycin, cephalexin, azithromycin, vancomycin, pentamidine, amoxycillin.

Combining the ICD-10 coding with hospital ADR, Burns, and HIV databases increased the likelihood of capturing all cADR episodes. Milder cADR may have been missed with this approach, although not the focus of this study. Although Australia does represent a multicultural "real world" setting, a predominance of Caucasian participants is noted. Concurrent infection in cases of AA-cADR is a confounder, although cADR-associated mortality was still higher in AA-cADR than NA-cADR. A limited number of cADR cases made interpretation of differences between AA-cADR types difficult.

CONCLUSIONS

We demonstrate that almost 50% of cADR are antibiotic related, in particular with beta-lactams, sulfonamides, and glycopeptides, associated with higher mortality, greater medical comorbidities, and more complex drug causality assessments. Although DRESS and AGEP were more frequently encountered in AA-cADR, mortality remained low. The variance of drug latency and antibiotic etiology for AA-cADR syndromes is informative to the clinician. The high rate of successful antibiotic "class" rechallenge in AA-cADR questions causality assessments and/or fears of allergy cross-reactivity. Further work is needed to ensure correct "allergy" labeling on discharge, whereas better diagnostics are required to aid complex AA-cADR drug causality assignment.

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