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Cutaneous Adverse Drug Reactions in a Tertiary Care Hospital

Dr.N.M Prasad Naik[1st], Dr.B.Raghu Kiran[2nd], Dr.Gautham K.Reddy[3rd]
[1st](Department of DVL, Osmania Medical College/ NTR University of Health Sciences, India)
[2nd](Department of DVL, Osmania Medical College/ NTR University of Health Sciences, India)
[3rd](Department of DVL, Osmania Medical College/ NTR University of Health Sciences, India)

Abstract: *Healthcare professionals, and indeed patients, face numerous challenges when considering ADRs. The objectives of this study is to observe the type, prevalence, and determine the severity index and causal relationship with final outcome of Cutaneous Adverse Drug Reactions and to recognize the offending drug. A Prospective observational, Non-invasive study was carried out at Department of Dermatology, Osmania General Hospital ,Hyderabad, India, a Tertiary Care Teaching Hospital for a period of 12 months. A total of 95 cases of suspected cutaneous ADRs were recorded, out of which 5 cases were excluded, remaining 90 cases were analyzed, among which one case was fatal leading to death. Maximum patients belonged to 21-30yrs, with female predominance. The most common pattern of cutaneous ADR observed was Steroid induced acne. The most common group of offending drugs were Topical corticosteroids. The results of assessment of the severity index revealed that most of the cases were moderate in severity. Clinical patterns and the drugs causing ADR are remarkably similar to those observed in other studies except for minor variations. It was evaluated that majority of the cases assessed were "probable", with few cases of "certain" using WHO and Naranjo's algorithm.*

Keywords – *Corticosteroids, Cutaneous Adverse drug reactions, Moderate, Naranjo's scale, WHO scale*

I. Introduction

Healthcare professionals, and indeed patients, face numerous challenges when considering ADRs; these include the desire to avoid or prevent ADRs in the first place, recognize ADRs when they do occur, and once recognized, manage them appropriately. Adverse Drug Reactions monitoring is a process of continuously monitoring of undesirable effect suspected to be associated with use of medicinal products. It facilitates collection of unbiased safety data observed during clinical practice in 'real life' circumstances. By implementing the ADR reporting, one can prevent further occurrence and promote awareness about drug safety and better patient care, among physicians, patients and other health care professionals.[1]

II. Aims and Objectives

2.1 To observe the types of Drug induced Cutaneous Adverse drug reactions (CADRs) in the patients attending the Dermatology Department.
2.2 To find out the Prevalence of Cutaneous Adverse drug reaction at Tertiary Care Hospital.
2.3 To determine causal relationship with final outcome of CADRs and to recognize the offending drug.
2.4 To determine the severity index of the adverse reactions.
2.5 To prevent CADRs and minimize hospitalization.
2.6 To achieve a better treatment outcome and improve productivity and health.

III. Materials and Methodology

3.1 Study Design

A hospital based Prospective, Observational; Non-invasive study was carried out on all the inpatients and outpatients attending the Dermatology department, Osmania General Hospital, Hyderabad for a period of 12months.

3.2 Inclusion Criteria

3.2.1 Patients of either sex as inpatients and outpatients attending Dermatology Department.
3.2.2 Patients more than 18 years of age.
3.2.3 All patients attending Dermatology department, presented with visible skin lesions suspected to be drug related included in the study

3.3 Exclusion Criteria:

3.3.3. Patients less than 18 years of age.
3.3.4. Patients without visible skin lesions.

3.3.5. Patients who could not recall the name of the suspect medicines consumed.
3.3.6. If lesions turned out to be disease related (e.g., viral exanthemas, rash of rickettsial infections, and collagen vascular disease,) on closer examination.
3.3.7. Patients who reported to have consumed indigenous (ayurvedic and homeopathic) medicines were also excluded.
3.3.8. Patients unable to respond to verbal questions.

3.4 Procedure for Data Collection and Analysis
The patients of either sex, in Dermatology Department are observed for Cutaneous Adverse events. , and are enrolled as per the inclusion and exclusion criteria.

3.5 Study Schedule and Plan
The patients were enrolled. Current medical history and diagnosis was noted during the first visit. After enrolment into study, follow up was done for the inpatients and outpatients (who were reviewed after a week). At each follow up patients are asked for any new complaints, and examined. Prescriptions, non-prescriptions and previous records are reviewed and Cutaneous Adverse drug reactions were analyzed and recorded in the proforma.

3.6 All this data are compiled in structured proforma, described as follows:
3.6.1 Patient Information
3.6.2 Description about Suspected Adverse Drug Reaction
3.6.3 Information about Suspected Drug
3.6.4 Assessment and Analysis of Adverse Drug Reaction
3.6.5 Information about the Assessor

IV. Results

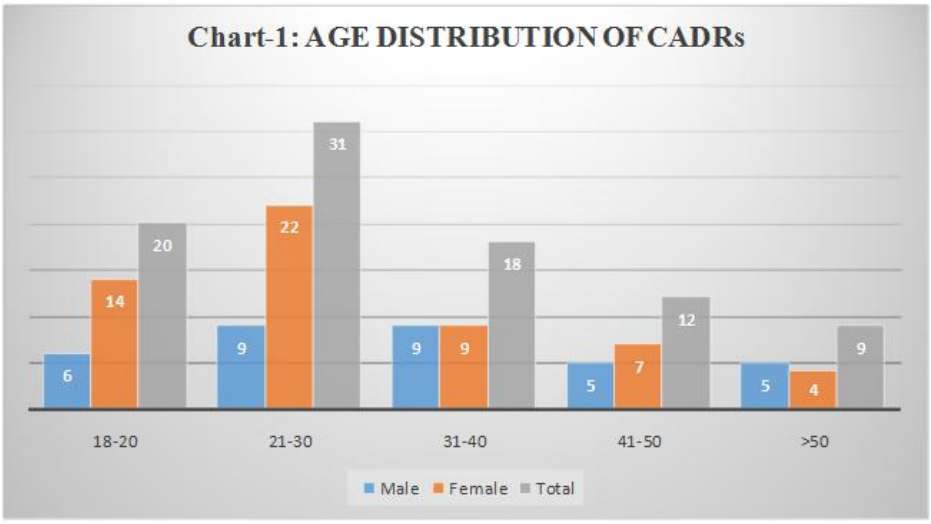
The data collected on CADRs form during the study period was analyzed into various parameters viz. Type of CADR, Causality and Severity assessments, clinical patterns of CADRs, detection of the offending drug implicated in the Cutaneous Adverse drug reaction and management of CADRs.

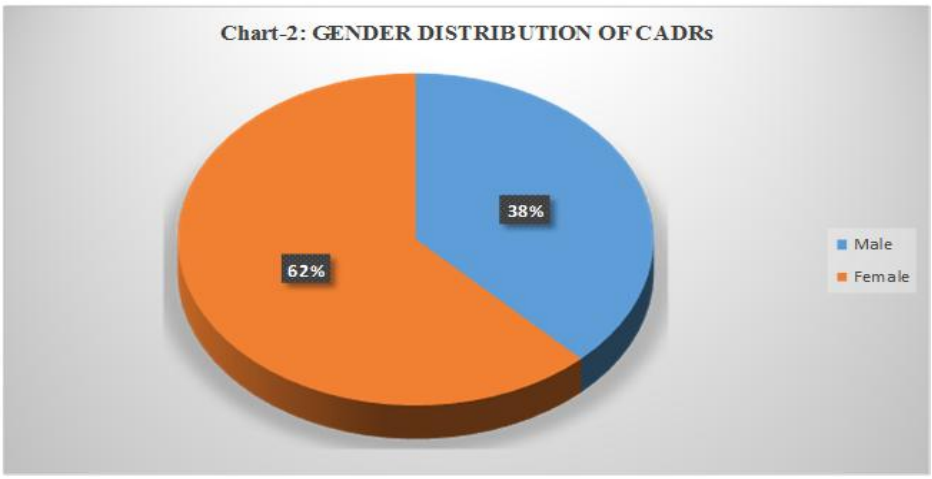
During the study period, September 2015 to August 2016, at Department of DVL, Osmania General Hospital, Hyderabad, a total of 95cases of suspected CADRs were recorded, out of which 5cases were excluded because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 90cases were analyzed, among which one case was fatal leading to death.

4.1 Age and Sex Distribution
Maximum incidence of CADRs was seen in age group 21-30 (34.4%) showing 31patients followed by 18-20 age group (22.2%), 31-40 age group (20%), 41-50 (13.3%) and >50(10%). The data revealed that 34cases(37.8%) were males and 56cases(62.2%) were females. Table-1, Chart-1 and Chart-2 shows details of age and sex distribution pattern of CADRs encountered during the study

Table-1: Age and Sex Distribution pattern of CARDs

Age group (in years)	No. of Male Patients	%	No. of Female Patients	%	Total	%
18-20	6	17.64%	14	25%	20	**22.2%**
21-30	9	26.48%	22	39.28%	31	**34.4%**
31-40	9	26.48%	9	16.07%	18	**20%**
41-50	5	14.7%	7	12.5%	12	**13.3%**
>50	5	14.7%	4	7.15%	9	**10%**
Total	**34**	**37.8%**	**56**	**62.2%**	**90**	**100%**



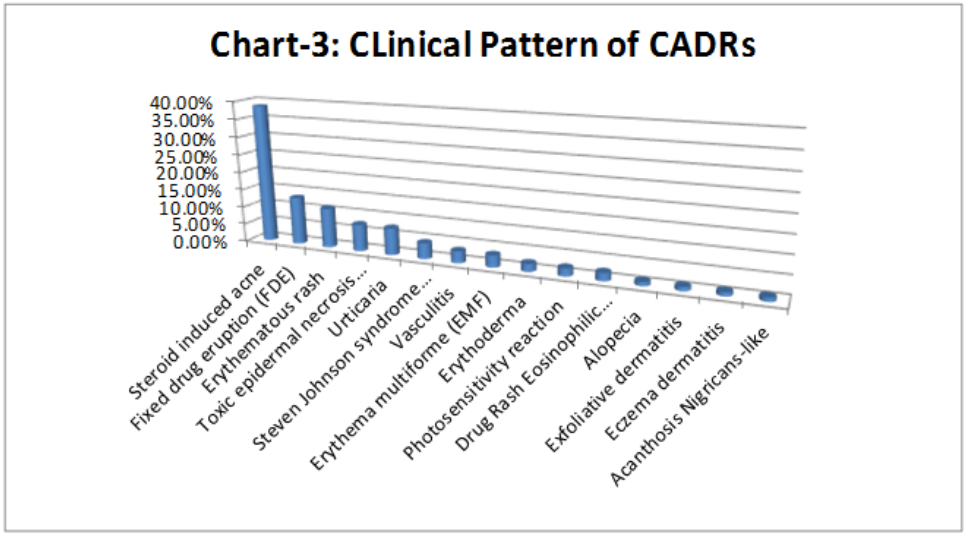


4.2 Clinical Patterns of CADRs

The most common pattern of CADRs observed was Steroid induced acne recording about 34cases(38.6%) followed by Fixed drug eruption(FDE) with about 12cases(13.3%), Erythematous rash showed 10cases(11.1%), Toxic Epidermal Necrosis(TEN) and Urticaria recording 7 cases each(7.5%), Steven Johnson Syndrome were identified in 4cases(4.4%), 3cases(3.3%) each of Vasculitis and Erythema was observed, 2cases(2.2%) each were seen with Erythroderma, Photosensitivity reaction and Drug rash eosinophilic systemic syndrome(DRESS) and Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis nigricans like each were identified in only 1patient(1.1%). The overall result showed female predominance. Table-2 and Chart-3 show details of the Clinical patterns of CADRs encountered during our study.

TABLE-2: CLINICAL PATTERNS OF CADRS

Clinical type	Frequency	Percentage
Steroid induced acne	34	38.6%
Fixed drug eruption (FDE)	12	13.3%
Erythematous rash	10	11.1%
Toxic epidermal necrosis (TEN)	7	7.5%
Urticaria	7	7.5%
Steven Johnson syndrome (SJS)	4	4.4%
Vasculitis	3	3.3%
Erythema multiforme (EMF)	3	3.3%
Erythroderma	2	2.2%
Photosensitivity reaction	2	2.2%
Drug Rash Eosinophilic Systemic Syndrome (DRESS)	2	2.2%
Alopecia	1	1.1%
Exfoliative dermatitis	1	1.1%
Eczema dermatitis	1	1.1%
Acanthosis Nigricans-like	1	1.1%



4.3 Drugs responsible for CARDs

The most common group of offending drugs responsible for CADRs were Topical corticosteroids recording 35cases(38.8%), among which Betamethasone recorded the highest incidence of CADRs identified in 24patients followed by Antibiotics with 22cases(24.8%), among which Ciprofloxacin was the common offending drug seen in 7patients followed by Metronidazole encountered in 6patients, Tetracycline in 4patients, Amoxicillin in 2patients, 1case was seen with each of Cotrimoxazole, Ceftriaxone and Dapsone. Use of tetracycline in one patient was fatal leading to death. Use of Anti-epileptic drugs was seen in 14patients(15.4%), where phenytoin recorded the highest number of ADRs. NSAIDs were seen in 9cases(10%), 3cases(3.3%) with Anti-tubercular drugs, Oral and Parentral corticosteroids with(3.3%). Rare cases(1.1%) were seen with, Antifungal(Fluconazole), Opioid Analgesic(Tramadol), Angiotensin converting enzyme inhibitors(ACEI) (Captopril), and Non-nucleoside reverse transcriptase inhibitor(NNRTI) (Efavirenz) about(1.1%).

Table-3 shows detail results of therapeutic drugs classes implicated in CADRs encountered in our study.

Table-3: Drugs Responsibleforcadrs

Drug class	Individual group	No. of cases	Total no. of cases	Percentage
Topical Corticosteroids	Betamethasone Mometasone Clobetasol	24 10 1	35	38.3%
Antibiotics	Ciprofloxacin Metronidazole Tetracycline Amoxicillin Cotrimoxazole Ceftriaxone Dapsone	7 6 4 2 1 1 1	22	24.8%
Anti-epileptics	Carbamazepine Phenytoin	2 12	14	15.4%
NSAIDS	Diclofenac sodium Naproxen Aspirin Ibuprofen	4 2 2 1	9	10%
Anti-tubercular	Isoniazid Rifampicin	1 2	3	3.3%
Oral/parenteral corticosteroids	Prednisolone(oral) Hydrocortisone(IV)	2 1	3	3.3%
Antifungal	Fluconazole	1	1	1.1%
Opioid analgesic	Tramadol	1	1	1.1%
Angiotensin converting enzyme inhibitor(ACEI)	Captopril	1	1	1.1%
(NNRTI)	Efavirenz	1	1	1.1%

4.4 Causality Assessment

4.4.1 Naranjo's scale

90cases of CADRs were analyzed. After assessment 2cases (2.2%) scored definite, with a score of +10. Remaining 88cases(97.8%) scored probable with 4cases scored +8, 44cases scored +7, 40cases scored +6. Unlikely, conditional or un assessable cases were excluded from the study.

4.4.2 WHO SCALE

After assessment 2cases(2.2%) scored certain, 88cases(97.8%) were of probable. Unlikely, conditional, unclassifiable were excluded from the study

Table-4 shows details of causality assessment of CADRs based on Naranjo's and WHO scale

Table-4: Causalityassessment of Cadrs (WHO and Naranjo's Causality Assessment Scale)

Type of reaction	WHO scale		Naranjo scale			
	No. of Cases	Percentage	No. of cases	Score		Percentage
Certain	2	2.2%	2	+10		2.2%
Probable	88	97.8%	88	No. of cases	Score	97.8%
				40 44 4	+6 +7 +8	
Possible	0	0%	0	0		0%

4.5 Severity Index of Cadrs as Per Hartwig's Assessment Scale

Severity of CADRs was assessed as per the Hartwig's classification graded on a 3-point scale. The results of assessment of the severity index revealed that most of the cases were moderate in severity accounting for 56cases(62.2%), followed by mild with 24cases(26.6%) and 9cases(10%) were identified as severe. One case (1.1%) was fatal leading to death.

Table-5 shows the details of severity assessment of CADRs encountered during the study period.

TABLE-5: Severity Index of Cadrs (Hartwig's Severity Assessment Scale)

Severity index	No. of cases	Percentage
Mild	24	26.6%
Moderate	56	62.2%
Severe	9	10%
Fatal	1	1.1%

V. Discussion

Adverse drug reactions (ADRs) constitute a major problem in society and in drug therapy, both as a health care problem and as an economic burden on society. They are a common cause of short-term hospitalization, prolonged hospitalization and death, especially among the elderly. Cutaneous ADRs have a varied presentation in clinical patterns, distribution of age and gender, Causality assessment and drug response because of variant geographical representation.

A Prospective, Observational and non-invasive study was carried out for a period of 6months recording 95cases, out of which 5cases were excluded because the offending drug was not identified or the data was insufficient to make any analysis. The remaining 90cases were analyzed, among which one case was fatal leading to death. Of the 90cases, 34(37.8%) were males and 56(62.2%) were females contributing to female preponderance, which as similar to that of studies reported in the literature by Ruchika Nandha, et al[2], V Sudershan et al[3], Saraswotineupane and Surya Raj Sharma[4], Akram Ahmed et al[5], Mahmood Farshchian et al[6]. Unlike in study of Shalini Chawla et al[7] and Tejas K Patel, Sejal H Thakkar, D C Sharma Review[8] which showed male preponderance.

In our study, highest percentage of CADRs was recorded in the age group of 21-30 showing 31patients (34.4%) followed by age group 18-20 with a total of 20patients (22.2%) and age group 31-40 with 18patients (20%). About 12patients (13.3%) were seen in age group of 41-50 and 9patients (10%) were seen in age group >50 which is in accordance with studies reported by Shalini Chawla et al[7] where the mean age of patients who experienced CADRs was 32, and V Sudershan et al[3] reported with higher incidence in adult age group between 21-30years.

Adverse drug reactions reported in our study showed maximum incidence with the application of Topical corticosteroids in about 35cases (38.8%), followed by Antibiotics in 22cases (24.8%), among which Ciprofloxacin was the common offending drug. 14cases (15.4%) were seen in patients who administered Anti-

epileptic drugs where phenytoin recorded the highest number of ADRs. NSAID was identified in 9cases (10%). Antitubercular, Oral and Parenteral corticosteroids were the offending agent observed in 3cases (3.3%). Rare cases (1.1%) were seen in patients taken Antifungal agents, Opioid Analgesic, Angiotensin converting enzyme inhibitors(ACEI), and Non-nucleoside reverse transcriptase inhibitor(NNRTI) about (1.1%). Studies carried out by Bharani Kalpana R, et al[1] have reported that oral Antimicrobials, Injectable Antimicrobials, NSAID's and Topical Steroids(Betnovate) were the leading cause of ADRs. All the other literature articles showed the highest offending drug to be Antimicrobials accounting for nearly 50% of the cases, followed by NSAIDs, Anti-epileptics. Among antimicrobials the highest was seen with fluoroquinolones according to the study by Dr.Reena Verma, Dr.Shreyansh Tiwari, et al[9], which can be correlated to our study showing 7cases with Fluoroquinolones.

The common clinical pattern of Cutaneous ADR observed in our study was Steroid induced acne recording about 34cases(38.6%) where 30cases were females and 4cases were males. The second common CADR was seen is Fixed drug eruption(FDE) with about 12cases(13.3%) encountering 4males and 8females, Erythematous rash Showed 10cases(11.1%) among which 6 were males and 4 were females. 7cases was seen each with Toxic Epidermal Necrosis(TEN) and Urticaria(7.5%). TEN showed about 5cases with female patients and 2cases with male patients, among which one was fatal observed in the female patient, where in similar mortality with TEN was seen in the study of Saraswotineupane and Surya Raj Sharma[4] Steven Johnson Syndrome were identified in 4cases(4.4%) where 2cases were seen in males and 1case in female. About 3cases(3.3%) of Vasculitis and Erythema was observed, Vasculitis showed female predominance where as Erythema multiforme showed male predominance. 2cases(2.2%) were seen with Erythroderma, Photosensitivity reaction and Drug rash eosinophilic systemic syndrome(DRESS). DRESS showed equal ratio of male and female patients. Photosensitivity reactions were seen in females and Erythroderma was seen in males. Alopecia, Exfoliative Dermatitis, Infectious eczema dermatitis, and Acanthosis were identified in only 1patient(1.1%). Unlike in other studies Fixed drug eruption was the highest recorded clinical pattern of ADR by Saraswotineupane and Surya Raj Sharma[4]. Some studies have observed urticaria and exanthematous rash as offending agents by Karamsad Suthar J and Desai S.V[10] recording both about 31.42%, where as studies by Balpande K.G., et al[11] recorded (32.75%) and (26.72%) respectively. Acute urticaria was the most common clinical presentation (59.2%) in the study by Mahmood Farshchian et al[6].

According to Causality assessment as per the Naranjo's scale, 2cases(2.2%) scored definite, with a score of +10. Remaining 88cases(97.8%) scored probable with 4cases scored +8, 44cases scored +7, 40cases scored +6, and as per the WHO scale 2cases(2.2%) scored certain, 88cases(97.8%) were of probable. Unlikely, conditional, unclassifiable were excluded from the study. Most of the studies showed the same assessment data giving high incidence of probable cases about (55.89%) reported by Mena Shrivastava et al[12], and about (90.62%) as reported by Palanisamy S, Arul Kumaran K S G, Rajasekaran A[13] and about (78.26%) reported by Himangshu Mahato et al[14].

The results of assessment of the severity index revealed most cases with moderate about 56cases (62.2%), followed by mild about 24cases(26.6%). 9cases(10%) were identified as severe. One case(1.1%) was fatal leading to death. Which was similarly seen in the study by Saraswotineupane and Surya Raj Sharma[5]. In our study all the cases were TypeB (Bizarre type) which was similarly seen in the study by Karamsad Suthar J.V1 and Desai S.V[10] where 100% ACDRs were TypeB (Bizarre immunological allergic drug reaction).

VI. Limitations

1.1 The short duration of our study was the major limitation. As a result, we could not get more data.

1.2 Poor knowledge about the awareness and importance of pharmacovigilance leads to huge under-reporting of ADR.

VII. Conclusion

The study has demonstrated that Cutaneous Adverse drug reactions have significant burden in terms of their impact on patient's lives, considering that there is relatively a high incidence of CADRs, therefore CADRs monitoring is of great clinical significance to prevent patient from unwanted exposure to drug toxicity. A wide clinical spectrum of cutaneous ADRs ranging from Steroid induced acne to Fixed Drug Eruption(FDE), Erythematous rashes, serious Toxic Epidermal Necrosis(TEN), Urticaria, Steven Johnson Syndrome(SJS) and Drug Rash Eosinophilic Systemic Syndrome(DRESS) was observed. Out of which Steroid induced acne was the most common cutaneous ADRs seen. Topical corticosteroids were the most common and among which Betamethasone was common offending agent causing CADRs. The study examined the perspective of the population showing that the highest prevalence of CADRs was seen in females thus concluding that females are at greater risk of developing CADR. The study shows that the significant impact of CADRs was among the age group 21-30years. The study demonstrated the causal relationship that was established using WHO and Naranjo's algorithm. It was evaluated that majority of the cases assessed were "probable", with few cases of

"certain". The analysis revealed the severity of Cutaneous ADR. It was assessed as per the Hartwig's classification graded on a 3-point scale showing majority of the cases as moderate followed by mild and severe. Fatal case was seen with TEN leading to death. The findings could be used as a framework for understanding patient experiences of other serious CADRs and to improve the future management of patients with these conditions. It can be used to guide the healthcare professionals to communicate more effectively regarding the management of such conditions. This helps in prevention and early detection of CADRs. The aim of the study was achieved by assessing the prevalence, causality and severity assessment, offending drugs involved in CADRs, clinical patterns recorded during the course of study. By implementing the ADR reporting, one can promote drug safety and better patient care, among healthcare professionals and be aware of these concerns so that they might be anticipated and addressed in future patients with CADRs.

VIII. Strategies to Prevent Cutaneous Adrs

An effective strategy to prevent the occurrence of ADRs is always preferred.
Some of the Measures that may reduce the occurrence of cutaneous ADRs are listed below.

- Avoid polypharmacy.
- Prescribe drugs, which have been known to cause cutaneous ADRs, only if extremely necessary.
- Obtain history of skin reactions in the past.
- Educate the patients regarding common early symptoms of drug reactions (e.g.erythematous rash, edema, urticaria, mucosal erosions, itching, burning of skin etc.) especially during start of a therapy.
- A patient with cutaneous ADRs should be provided with a card or prescription containing the name(s) of offending agents.

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