

Management of epidermal growth factor receptor inhibitor-associated rash: a systematic review

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Cancer patients treated with epidermal growth factor receptor inhibitors (EGFRIs) frequently experience skin toxicities (rash) that can compromise their quality of life and lead to dose reduction or discontinuation of treatment. Reflecting the need for effective management of EGFRi-associated rash, a number of clinical practice guidelines and management recommendations have been developed. The objective of this systematic review is to identify and summarize all available published recommendations of rash management strategies and evaluate their basis of evidence, to describe consensus in the recommendations, and where there is a lack of consensus to describe the opportunities for future clinical research to improve clinical practice in the management of EGFRi rash. Fifty-nine articles published from 2005-2011 were selected for inclusion in the systematic review. Common drug recommendations were oral and topical antibiotics, topical corticosteroids, and antihistamines; low-grade rash was generally recommended to be managed with topical antibiotics or corticosteroids, grade 2 rash with oral antibiotics or antihistamines, and severe grades of rash with oral corticosteroids or delay/dose reduction of EGFRi. The focus of clinical practice guidelines and recommendations was on reactive management. A better understanding of pre-emptive versus reactive treatment with the implementation of appropriately designed randomized controlled studies could support a more effective management of EGFRi-associated rash and improve patient outcomes. Consideration of patients' self-reported outcomes and consistent grading of rash toxicity are also recommended. **Funding/sponsor** Eli Lilly & Co, Bristol-Myers Squibb

Epidermal growth factor receptor inhibitors (EGFRIs) are targeted agents that are widely used to treat a range of tumor types including non-small-cell lung cancer, colorectal cancer, pancreatic cancer, and head and neck cancers. Treatment-emergent adverse events associated with EGFRi use include characteristic skin toxicities and affect roughly half of all patients treated with EGFRIs, with around 10% or more of these patients experiencing serious events of grade 3 or above. The precise incidence and severity of rash are difficult to ascertain, in part because the terminology used to describe EGFRi-associated rash varies widely.¹⁻³

EGFRi-associated rash can severely compromise patient quality of life, resulting in substantial physical discomfort and limitation in daily activities and independence.⁴⁻⁹ The appearance of rash may also be associated with profound psychological impact,¹⁰ and in the context of controlled clinical studies, these effects have led to dose reduction^{4,11-13} or discontinu-

ation of treatment.¹⁴⁻²⁵ Currently marketed EGFRi treatments also include specific guidance for therapy interruption or dosage adjustment in case of rash or other dermatologic toxicity.²⁶⁻²⁹ Effective rash management therefore seems necessary to realize the benefit of EGFRi treatment and to minimize negative effects on patient quality of life.

To the knowledge of the authors, there are no published studies that comprehensively assess the consistency of rash management recommendations. The objective of this systematic review is to identify and summarize all available published recommendations of rash management strategies and evaluate their basis of evidence. Where possible, this review seeks to describe any consensus in rash management recommendations, and where there is a lack of consensus, to describe opportunities for future clinical research with the potential to improve clinical practice in the management of EGFRi rash and ultimately to improve patient outcomes.

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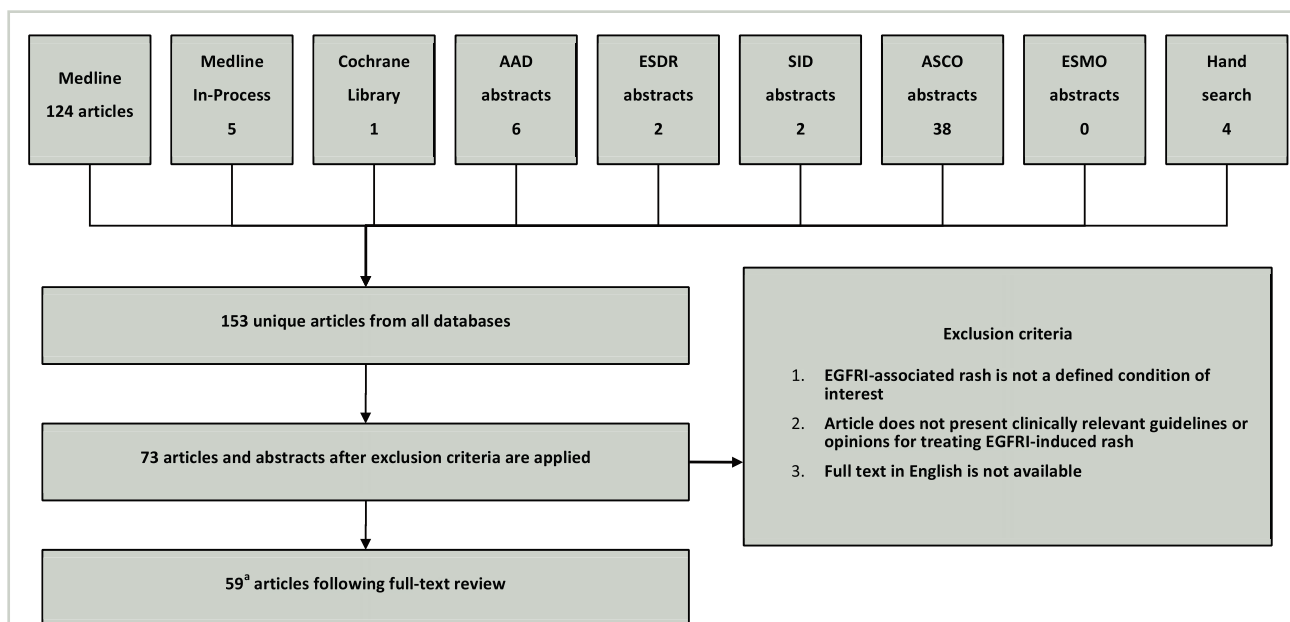


FIGURE 1 Schematic overview of the systematic review

AAD, American Academy of Dermatology; ESDR, European Society for Dermatological Research; SID, Society for Investigational Dermatology; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology

^aThe 59 included articles were obtained after applying exclusion criteria to the full-text of the 73 articles.

Methods

Data sources and searches

Searches were performed in June 2011 in several publication and congress databases (Figure 1). The searches were limited to articles published from 2005–2011 in the Medline, Medline In-Process, Cochrane Library, American Academy of Dermatology, Society for Investigative Dermatology, and American Society of Clinical Oncology databases. Searches in the European Society for Dermatological Research database included abstracts published from 2005–2010 (the most recent available). Searches in the European Society for Medical Oncology abstract collection was done by hand and included articles published from 2002–2010 (the most recent available). In addition, 4 articles referenced in selected articles that were deemed to be relevant but were not identified in any of the database searches were added by hand.

Selection of relevant articles

To be included in the review, the articles were required to fulfill 3 criteria:

- EGFR-associated rash was the defined condition of interest;
- Clinically relevant guidelines or opinions for treating EGFR-associated rash were presented; and
- The full text in English was available.

Results included diverse article types, including reviews, case reports, and both prospective and retrospective studies (Figure 1, Table 1; Online Table 1-keywords).³⁰

Data extraction, quality assessment, and analysis

Articles were classified according to article type, region/perspective, rash management strategies, grade, EGFR treatment or treatments, and evidentiary basis for conclusion. The study description/design, results, and authors' conclusions were also noted. Articles of primary research were mutually exclusively classified either as a case report, a prospective study (not a randomized controlled trial), a retrospective study, a randomized controlled trial (RTC) or a cross-sectional survey. Clinical practice guidelines were described as articles that contained systematically developed recommendations or management strategies produced under the auspices of medical specialty associations, relevant professional societies, government agencies or health care organizations or plans. If an article fitted the description of a clinical practice guideline, then it was not counted as a review article (Online Table, characteristics for all 59 articles). All data were separately extracted by 2 of the authors (PS, KY) and differences were adjudicated. Descriptive analysis using counts of article characteristics, which included study type, cancer type, and region of focus, and management strategies was performed using Microsoft Excel.

Results

A total of 153 articles were identified by the search strategy. The full text of 73 articles was reviewed, and after apply-

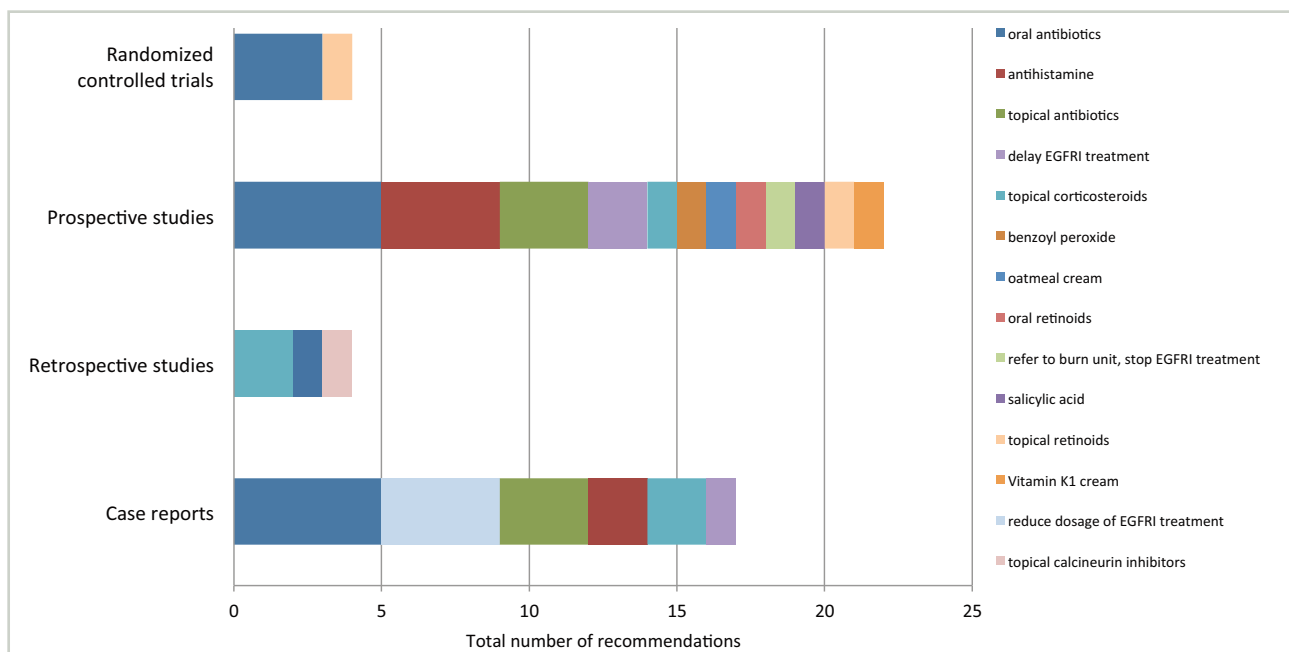


FIGURE 2 Rash management interventions by primary data source (excluding review articles, surveys, and clinical guidelines; n = 20 articles.) Counts indicate the number of articles that recommend a particular rash management intervention. A single article may have multiple recommendations.

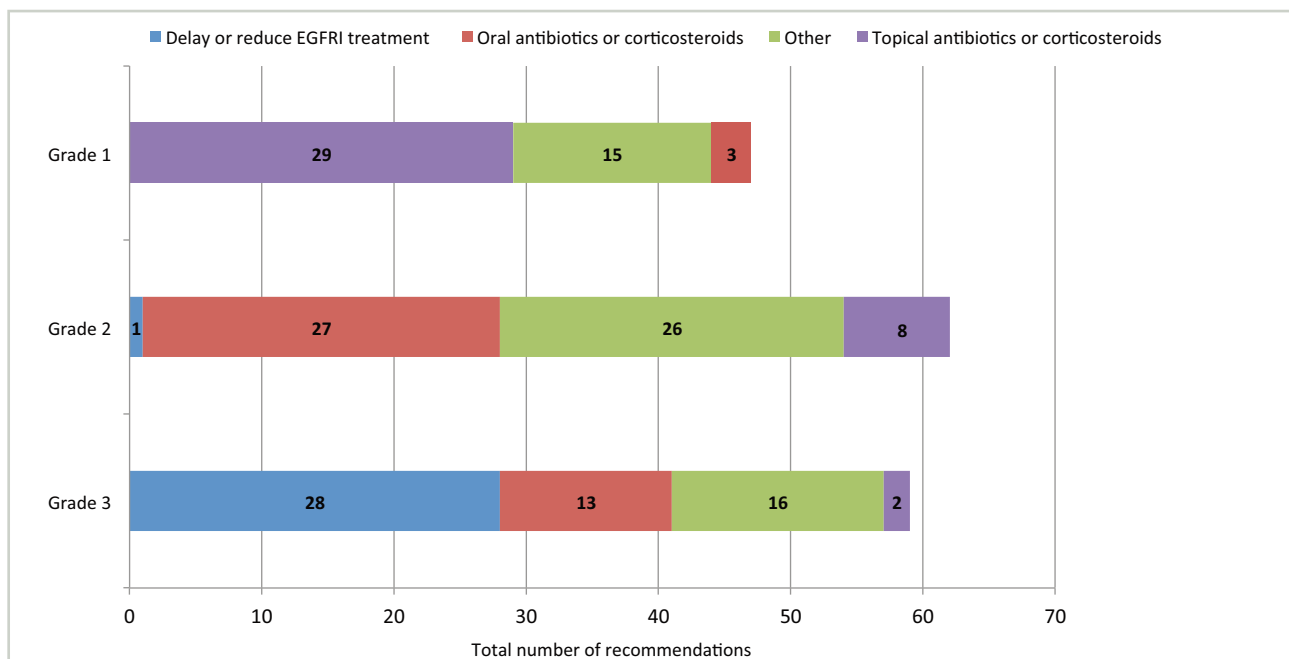


FIGURE 3 Management recommendations by severity of rash (n = 35 articles). Counts indicate the number of articles that recommend a particular rash management intervention. A single article may make multiple recommendations or may recommend a given intervention for multiple grade-specific treatments other than antibiotics or corticosteroids.

ing exclusion criteria, a total of 59 articles were selected. Articles published between 2005 and 2011 providing rash management recommendations were included in the review (Figure 1). None of the review articles were sys-

tematic reviews. The articles identify a total of 20 different types of rash management treatments (Table 2). Most of the articles were from Europe (18) and the United States (34).

TABLE 1 Classification of articles identified in the systematic review

Article type	Count
Review article	19
Clinical practice guideline	18
Case report	7
Prospective study (non-RCT)	7
Retrospective study ^a	3
RCT ^o	3
Cross-sectional survey ^b	2

RCT, randomized-controlled trial

^aRetrospective studies include 3 chart review studies. ^bThe surveys include 2 cross-sectional surveys of oncologists or other health care practitioners involved in rash management.

Rash management interventions

Regardless of grade of rash, the most commonly identified drug interventions within the selected publications include oral antibiotics, topical antibiotics, topical corticosteroids, and antihistamines (Table 2). Less common recommendations include oral corticosteroids, topical calcineurin inhibitors, oral retinoids, topical retinoids, benzoyl peroxide, anti-agents, and salicylic acid. Changes to EGFRi treatment are frequently recommended for severe rash, including delay, stopping treatment, or dose reduction.

A range of evidence sources were cited for rash management recommendations given in the 59 articles. Expert opinion was the most common evidentiary basis for recommendations. In addition, various primary research studies were identified, including RCTs, other interventional, prospective studies without a comparator arm, case report studies, and other retrospective studies. Figure 2 presents rash management intervention recommended by study design for the subset of primary research articles identified in the literature search.

As highlighted above, most of the articles identified in our search recommended both topical and oral antibiotic treatments. All 3 RCTs³¹⁻³³ and 5 of the 7 studies with other prospective designs supported their use.³⁴⁻³⁸

Topical corticosteroids were recommended as a rash management intervention in 24 of the 59 articles identified in this review, however, relatively little clinical evidence was identified to support this recommendation. Topical and oral retinoids are also recommended for rash management (Table 2), although they are less often recommended than antibiotics or corticosteroids.^{39,40,33,35} Other, more unconventional treatments were also identified in the literature. Benzoyl peroxide was recommended based on 1 prospective study³⁵ and 1 review article citing anecdotal reports,⁴¹ but specifically not recommended in 2 recent reviews.^{2,3}

Topical wound gel decreased the itching sensation in a prospective study of 13 patients with a grade 2 rash.⁴² Vitamin K cream allowed 69.2% of patients good skin-rash symptom control in an uncontrolled prospective study.³⁴ In another uncontrolled prospective study, 43 treatment with topical oatmeal cream was associated with full-rash resolution in 64.3% of patients, partial improvement in 35.7%, and overall response in 100% of patients who applied colloidal oatmeal lotion 3 times a day for 21 days.

Reactive management by severity of rash

Most of the 59 identified articles provide EGFRi-associated rash management strategies based on the severity of rash, including 27 of 37 review articles or clinical guidelines. Table 2 summarizes all recommendations for use of specific rash management interventions by grade of rash. These data illustrate a pattern of escalating rash management interventions by severity of rash: topical treatments are mostly recommended for grade 1 rash, oral treatments are mostly recommended for more severe rash, and delay or dose reduction of EGFRi are almost exclusively recommended for grade 3 rash (Figure 3).

Pre-emptive rash management

The timing of treatment may be important for effective rash management. Three RCTs evaluated preventing the onset of EGFRi-associated rash by using oral antibiotics prior to the onset of rash.³¹⁻³³ All three RCTs found that pre-emptive oral antibiotics were well tolerated and showed signs of reducing severe skin toxicities, however, future studies are necessary to conclude whether this strategy prevents EGFRi rash. Only 1 of these RCTs compared the use of pre-emptive and reactive treatments.³¹ All 3 studies demonstrated that pre-emptive antibiotic treatment may decrease severity or incidence of rash,^{31,33} although 1 did not reach statistical significance.³³

All of the other primary research articles focused on reactive rash management.^{34-38,42-43} Review articles and clinical guidelines often recommend early intervention to prevent worsening of rash, but while some guidelines strongly recommend pre-emptive use of oral antibiotics,³ other recent articles either do not discuss this approach^{44,45} or review the literature, but do not recommend this management strategy based on the available evidence.^{2,46}

Variation among management recommendations

Despite a general trend by severity emerging in the rash management recommendations, Table 2 shows that substantial variation in these recommendations does exist within each grade of rash. Recommended treatments are also not always restricted to a grade of rash. Oral antibiotics are, for example, the most commonly recommended rash management intervention for grade 2 rash, but also are recommended for grade 1 and grade 3 rash, and a total of

TABLE 2 Recommendations for managing EGFR-associated rash based on grade (n = 59 articles)^a

Rash management intervention	Rash grade						Total
	I	II	III	IV	All	Unspecified	
Oral antibiotics	4	23	2		3	13	45
Topical antibiotics	22	4	1			11	38
Topical corticosteroids	8	4	1		1	12	26
Antihistamines		13	3			5	21
Delay EGFR treatment			17	1		1	19
Oral corticosteroids		3	8	2		2	15
Reduce dosage of EGFR treatment		1	8			4	13
Oral retinoids	1	1	4			2	8
Topical calcineurin inhibitors	1	4			1	2	8
Refer to burn unit, stop EGFR treatment				8			8
Topical retinoids	1	2	1			2	6
Benzoyl peroxide	4	1				2	7
Compresses		1	5			1	7
Stop EGFR treatment			2	4			6
Anti-rosacea agents	4						4
Oatmeal cream	2					2	4
Salicylic acid	2	1				1	4
Vitamin K cream		2					2
Drying pastes			1				1
Hydrophilic dressings			1				1

EGFR, epidermal growth factor receptor inhibitor.

^aCounts indicate the number of articles that recommend a particular rash management intervention. A single article may make multiple recommendations or may recommend a given intervention for multiple grades of rash.

16 articles recommend use of oral antibiotics unspecified by any particular grade (Table 2).

Some variation was observed in recommendations by article type. Seven of the 18 clinical practice guidelines were self-identified as consensus guidelines, incorporating recommendations from multidisciplinary teams that include radiation oncologists, medical oncologists, pharmacologists, and dermatologists.^{2,45,47-49} Although the consensus guidelines' recommendation to use oral treatments for higher grades of rash is consistent with other article types, consensus guidelines were the only article type that recommended oral steroids more frequently than oral anti-

biotics across all grades of rash.

There was substantial variation in the terminology used to describe EGFR-associated rash, which was cited in several articles as a potential source of variation in treatments recommended by grade of rash.⁴⁹⁻⁵³ The Common Terminology Criteria for Adverse Events (CTCAE) is frequently used within the context of phase 2 and 3 clinical trials investigating the efficacy of EGFR therapy. Even when the CTCAE system is used, different rash descriptions can be reported; for example, separate descriptions exist for rash, skin rash, acneiform, acne-like rash, skin toxicity.⁵¹ Also variations in the rash grading system can

be found between different versions of the CTCAE.^{54,55} The Medical Dictionary for Regulatory Activities^{8,13-14,56-58} is also often used to classify the grade of rash as well as other systems such as the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).¹⁵ Notably, the severity and outcomes of rash management interventions typically relied on a physician's assessment.

Discussion

The objective of this systematic review was to identify and summarize all available published recommendations of rash management strategies and evaluate their basis of evidence. Fifty-nine articles were found, which included clinically relevant guidelines or opinions for treating EGFR-associated rash. Most of the recommendations were based on expert opinion; consequently, quality scoring and meta-analysis of the data extracted from these articles were not conducted. Otherwise, PRISMA guidelines were followed for reporting this systematic review.³⁰

Of the 19 review articles identified by our search, none were systematic reviews. The reviews did not comprehensively describe the existing literature nor did they summarize or analyze the trends in management recommendations described in the literature. Eighteen clinical practice guidelines for the effective management of EGFR-associated rash were also identified. The focus of the guidelines was on the reactive management of EGFR-associated rash.

The 59 articles, identified by the systematic search, presented a range of management recommendations. The most commonly recommended drug interventions were oral antibiotics, followed by topical antibiotics, topical corticosteroids and antihistamines. Although there was variation in treatments recommended for each grade of rash, a general pattern of rash management recommendation by grade did emerge, however the lack of consistency in grading may impact these results. It was generally recommended that a low grade of rash is managed with topical antibiotics or corticosteroids, grade 2 rash is managed with oral antibiotics or antihistamines, and more severe grades of rash are managed with oral corticosteroids, and delay or dose reduction of EGFR. EGFR product labeling is consistent with recommendations for dose modification and therapy interruption for severe rash.²⁶⁻²⁹

Evidence supporting the use of oral corticosteroids is more limited. None of the identified prospective studies evaluated the effectiveness of oral corticosteroids in managing EGFR-associated rash. Oral corticosteroids carry risks, and can increase the risk for infection for many patients³ and could potentially interfere with the activity of the 2 EGFR treatments, cetuximab and panitumumab.^{48,50}

With the exception of the pre-emptive strategies using oral antibiotics and topical corticosteroids and retinoids, the efficacy and tolerability of these management strategies have not been evaluated in the context of a con-

trolled trial. Only 3 RCTs were identified by our systematic review.³¹⁻³³ We may not have identified all the RCTs evaluating rash management programs as the focus of our search strategy was not randomized controlled studies of rash management options, rather it was limited to clinically relevant guidelines or opinions for treating EGFR-associated rash. Nonetheless, the finding that there is a paucity of RCT-based evidence is consistent with the comments found in the literature.³ The focus of the RCTs was on pre-emptive management of EGFR-associated rash. One of the 3 trials compared pre-emptive management with reactive management, and suggested that pre-emptive treatment is much more effective than reactive treatment at reducing the incidence of grade 2 or higher rash.³¹ With limited information and a lack of phase 3 data, a better understanding of the effectiveness of pre-emptive versus reactive strategies with the implementation of appropriately designed RCTs could support a more effective management of EGFR-associated rash and potentially improve patient outcomes.

One important outcome to consider in the design of future trials is patients' self-reported outcomes, such as symptoms or health-related quality of life. While the physical appearance of rash in terms of incidence and severity is a relevant outcome, the clinician's interpretation of the implications for the patient is not necessarily a good reflection of how the patient feels or perceives the severity of rash. A more consistent and precise measurement of the manifestations of rash incorporated in the design of future clinical trials would also help support the selection of alternative rash management strategies.

There is some debate and speculation over the presence of rash being associated with the efficacy of EGFR therapy.^{51,52} If this association was to be confirmed with further research, the need for a better understanding of the effectiveness of reactive versus pre-emptive EGFR-associated rash management strategies would nonetheless remain. Moreover, it would be of interest to investigate whether effective rash management affects the efficacy of EGFR therapy.

A possible limitation of this review results from the inclusion of recommendations from review articles and guidelines as well as clinical studies. As such, it did not systematically search for primary research studies and may have omitted some relevant studies. Although the classification of study type is mutually exclusive there is some overlap in the studies cited by the review articles and guidelines and the primary research articles. The guidelines, however, relied mainly on expert opinion and there was generally a paucity of primary research data. In addition, some general, typically preventative, nonprescription interventions ("tips") were also not specifically captured, including limiting sun exposure, using sunscreen, avoiding skin irritants, and so on.^{35,54,59} Nonetheless, we believe that the key conclusions of this analysis are robust to these limitations.

Conclusions

Most management recommendations relied on expert opinion. Although there was variation in recommendations, it was generally recommended that low grade of rash is managed with topical antibiotics or corticosteroids, grade 2 rash with oral antibiotics or antihistamines, and more severe grades of rash with oral corticosteroids, and delay or dose reduction of EGFR. A better understanding of pre-emptive versus reactive treatment with the implementation of appropriately designed randomized con-

trolled studies could support a more effective management of EGFR-associated rash and improve patient outcomes. A consistent grading of rash toxicity is necessary to accurately assess the severity of rash and guide the development of rash management strategies.

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