Gloucestershire Hospitals NHS Foundation Trust

MANAGEMENT OF SKIN TOXICITY RELATED TO PARENTERAL ANTI-EGFR TREATMENT FOR COLORECTAL PATIENTS

PATIENTS All adult patients prescribed Cetuximab or Panitumumab

Epidermal Growth Factor Receptor (EGFR) inhibitors are commonly used in the treatment of colorectal, head & neck, lung and pancreatic cancers. These treatments are associated with a variety of skin toxicities including an acneiform rash, dry/itchy skin, paronychia or abnormal hair growth. Of note, the presence of skin toxicity has shown to be positively correlated with treatment response[1].

Approximately 90% of patients experience some degree of skin toxicity whilst on anti-EGFR treatments[2]. The most common of these is an acneiform rash, which occurs in 60-80% of patients and usually appears in the first 1-2 weeks of treatment[3]. Skin toxicity can have a significant impact on patients' quality of life and may affect treatment adherence. Prophylactic treatment has been shown to reduce the severity of skin toxicity compared with reactive management[4]. It is therefore important to adequately counsel patients prior to initiating therapy and to provide the correct supportive medications.

Prior to cycle one of EGFR inhibitor

The following advice should be given to patients prior to commencing treatment in order to minimise skin toxicities. This may require a second pre chemo education appointment if chemotherapy is initiated before RAS status, ie suitability for EGFR inhibitor, is known.

Skin:

- Use sunscreen daily (SPF≥15)[4] and avoid direct sunlight
- Use tepid water to wash and avoid hot baths/showers
- Avoid drying skin-care products e.g. avoid fragranced moisturisers and soaps, use gentle shampoos
- If using cosmetics, use hypoallergenic products, but even these may exacerbate symptoms

Nails:

- Apply petroleum jelly around nail beds overnight
- Avoid manicures and pedicures
- Avoid tight fitting shoes

Education on recognition of skin toxicities and where to get help:

- Colorectal specialist nurses
- Acute oncology unit
- Provide patient with skin reaction patient information booklet to aid telephone consultations

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Patients with pre-existing conditions e.g. patients with current rosacea, acne, active eczema

- May need immediate referral to Dermatology for management

All patients started on anti-EGFR should be prescribed:

- A light emollient, such as Aveeno or Epimax original Cream
- A soap substitute – Aveeno or Epimax original Cream can be used as a soap substitute **Emollients are not recommended to be used as soap substitutes during COVID-19 pandemic**[6]. Option to escalate to Dermol 500 lotion if skin infection present or QV gentle wash if emollient as a bath additive if not tolerated. [7]
- Doxycycline 100mg OD – prophylaxis (to be taken throughout treatment)
  (If allergic to tetracyclines then consider clarithromycin 250mg BD unless patient is receiving Irinotecan or Encorafenib as both can prolong the QT interval if this is the case then consider treatment without prophylactic antibiotics)
- Mild topical steroid Hydrocortisone 1% ointment OD
  (For use if symptoms arise, short term use)

From cycle two onwards

Skin toxicities should be graded according to the table below and treatment escalated according to severity. Please see *Appendix 3* for Common Terminology Criteria for Adverse Events (CTCAE) grading system.

	Grading of skin toxicity		
	Mild (1)	Moderate (2)	Severe (3)
Impact on Quality of Life	Not limiting day-to-day activities	Limiting certain daily activities	Intolerable to patient
Intervention required	Can be self-managed by the patient	Requires several treatments to manage	Requires intensive local and possibly systemic treatment to manage
Ability to continue EGFR treatment	No dose modification required	No dose modification required	Treatment discontinuation until symptoms improve to mild/moderate
Skin: Acneiform	Papules and pustules	Papules, pustules and irritation	Crusted, eroded pustular acneiform lesions
Skin: Xerosis	Redness and flushing +/- itch/Dry, scaly skin	Dry, scaly skin with itch	Extensive dry, scaly skin with itch
Nails	Nail-fold oedema or erythema; disruption of the cuticle	Oedema or erythema with discharge or nail plate separation resulting in discomfort	Oedema or erythema with discharge or nail-plate separation resulting in severe pain and reduced mobility

Acneiform rash:

Mild

- Mild topical steroid Hydrocortisone 1% ointment OD
- Continue oral Doxycycline at 100mg OD
- For scalp lesions, prescribe Betamethasone 0.1% ointment OD

Moderate

- As above, plus:
  - Increase dose of Doxycycline to 100mg BD for 4 weeks
  - For scalp lesions, step up to Dermovate ointment OD

Severe

- Hold treatment until symptoms have resolved to mild or less
- Consider dose reduction
- Escalate to a moderate steroid Eumovate ointment OD
- Seek dermatology advice

Xerosis:

Mild

- Increase frequency of emollient application
- Consider switching to heavier emollient e.g Zerodouble gel or Epimax ointment
- Hydrocortisone 1% ointment OD to affected areas

Moderate

- Consider switching emollients to an ointment
- Steroid ointment to affected area (Eumovate ointment OD)
- For itch, consider prescribing Cetirizine 10mg OD PRN or hydroxyzine 25mg ON (sedating).
- Note: benefit in xerosis is minimal

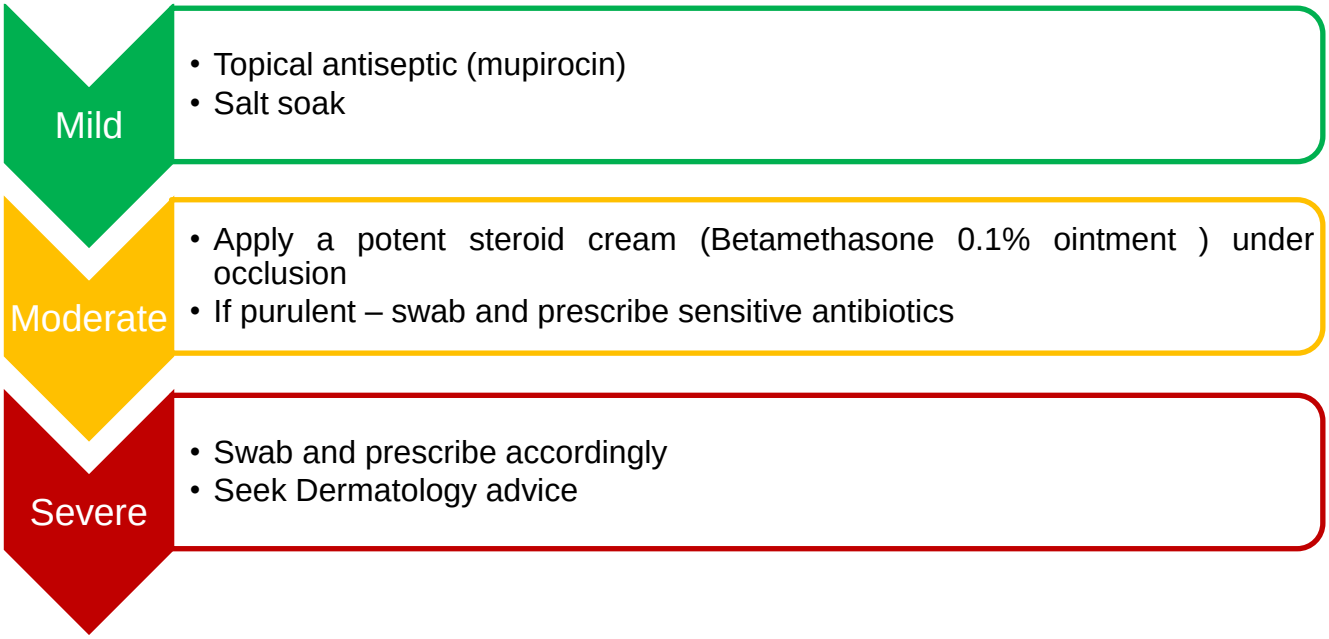
Severe

- More potent steroid (Elocon ointment OD - Not to face, continue Eumovate here)
- Consider dose reduction
- Seek Dermatology advice

Very Severe

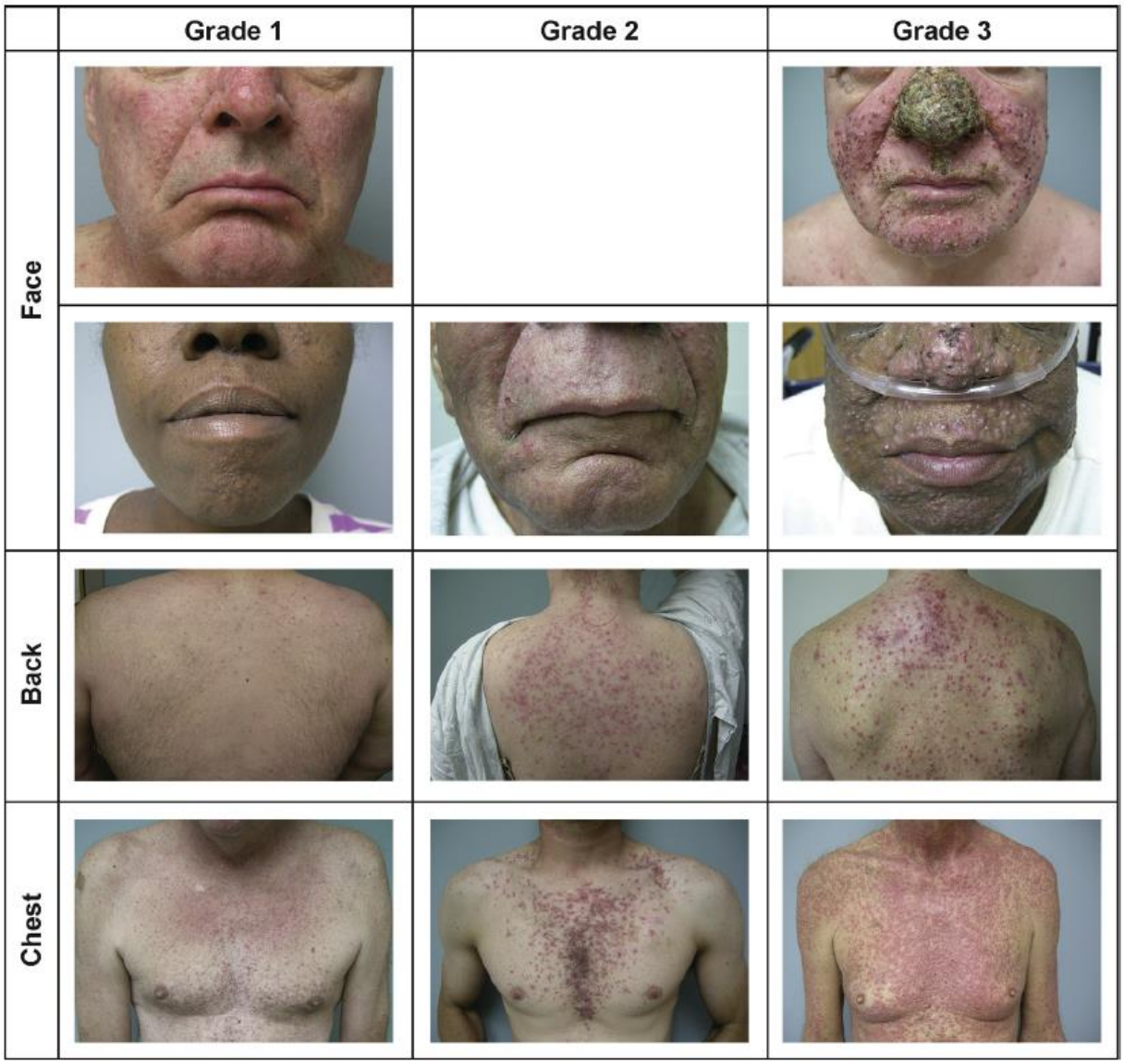
- Once maximal topical therapy has been used consider introduction of oral steroids

Nails:


Mild
• Topical antiseptic (mupirocin)
• Salt soak
Moderate
• Apply a potent steroid cream (Betamethasone 0.1% ointment) under occlusion
• If purulent – swab and prescribe sensitive antibiotics
Severe
• Swab and prescribe accordingly
• Seek Dermatology advice

Appendix 1.

Photographs of Skin Rash Occurring During Anti-epidermal Growth Factor Receptor Monoclonal Antibody Treatment

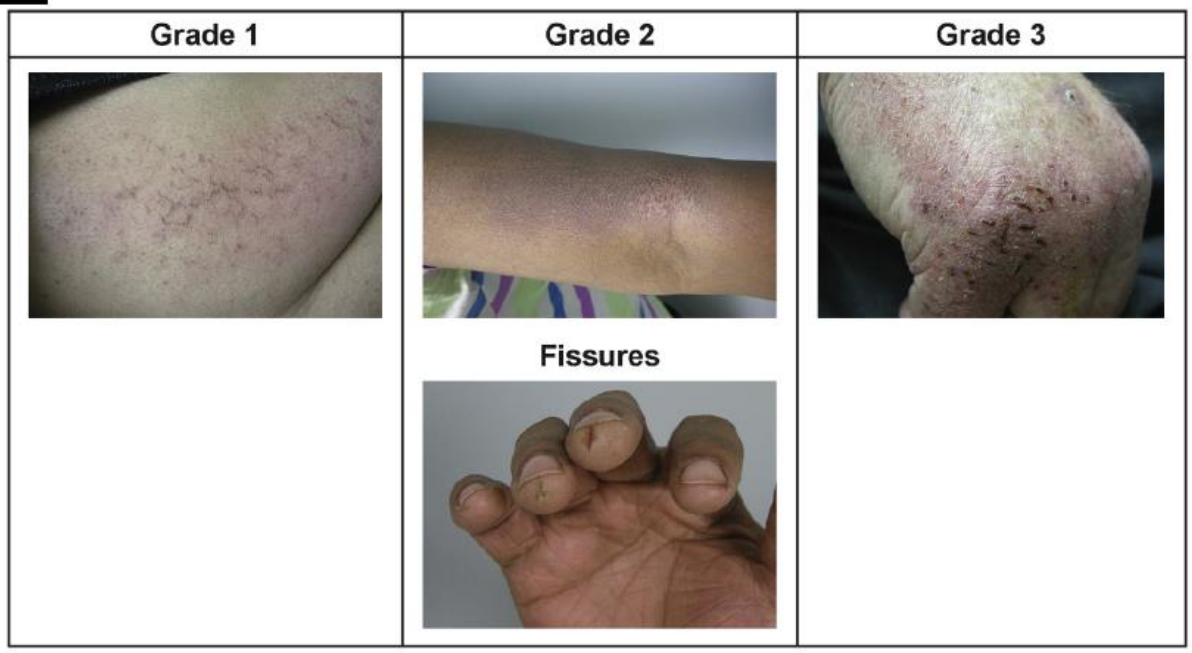


Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic toxicity occurring during anti-EGFR monoclonal inhibitor therapy in patients with metastatic colorectal cancer: a systematic review. Clinical colorectal cancer. 2018 Jun 1;17(2):85-96.

Reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acneiform rash	Pustules/papules covering <10% BSA +/- pruritis or tenderness	Pustules/papules covering 10-30% BSA; psychosocial impact & limiting instrumental activities of daily living	Pustules/papules covering >30% BSA; limiting self-care activities of daily living; associated with local superinfections with antibiotics indicated	Papules/pustules covering any percentage BSA; extensive superinfection with intravenous antibiotics indicated; life-threatening consequences	Death

Photographs of (A) Xerosis and (B) Paronchyia Occurring During Anti-Epidermal Growth Factor Receptor (EGFR) Therapy by Grade. The First Symptoms for Xerosis (ie, Rough, Dry Skin) Typically Occur Within 1 to 2 Months of Initiation of anti-EGFR Therapy. Paronchyia (ie, Inflammation of the Nail Folds of the Fingernails and Toenails) Can Lead to Infection and Swelling/Tenderness and Usually Develops After Skin Reactions, Within 20 Days to 6 Months After Treatment Initiation

A



B

Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic toxicity occurring during anti-EGFR monoclonal inhibitor therapy in patients with metastatic colorectal cancer: a systematic review. Clinical colorectal cancer. 2018 Jun 1;17(2):85-96.

Reaction	**Grade 1**	**Grade 2**	**Grade 3**
Xerosis	Covering <10% BSA and no associated erythema or pruritis	Covering 10-30% BSA and associated with erythema or pruritis; limiting instrumental activities of daily living	Covering >30% BSA and associated with erythema or pruritis; limiting instrumental activities of daily living
Paronychia	Nail fold oedema or erythema; disruption of the cuticle	Localised intervention indicated; oral intervention indicated (e.g. antibiotic, antifungal, antiviral), nail fold oedema or erythema with pain associated with discharge or nail plate separation; limiting instrumental activities of daily living	Surgical intervention or IV antibiotics indicated; limiting self-care activities of daily living

Appendix 2.

Common terminology criteria for adverse events (version 5.0)[6]					
Reaction	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental activities of daily living			

References:

1. Perez-Soler, R., Saltz, L., 2005. Cutaneous Adverse Effects With HER1/EGFR-Targeted Agents: Is There a Silver Lining? Journal of clinical oncology. 1;23(22):5235-46

2. Lacouture, M., Anadkat, M., Jatoi, A,., Garawin, T., Bohac, C., Mitchell, E., 2018. Dermatologic Toxicity Occurring During Anti-EGFR Monoclonal Inhibitor Therapy in Patients With Metastatic Colorectal Cancer: A Systematic Review. Clinical colorectal cancer. Volume 17, no.2, 85-96.

3. Beech, J., Germetaki, T., Judge, M, Paton, N., Collins, J., Garbutt, A., Braun, M., Fenwick, J., Saunders, M., 2018. Management and grading of EGFR inhibitor-induced cutaneous toxicity. Future Oncology; 14(24):2531-2541

4. Lacouture, M., Mitchell, E., Piperdi, B., Shearer, H., Iannotti, N., Xu, F., Yassine, M., 2010. Skin Toxicity Evaluation Protocol With Panitumumab (STEPP), a Phase II, Open-Label, Randomized Trial Evaluating the Impact of a Pre-Emptive Skin Treatment Regimen on Skin Toxicities and Quality of Life in Patients With Metastatic Colorectal Cancer. Journal of Clincal oncology 28:1351-1357

5. National Eczema Society, 2020. Advice on coronavirus (COVID-19) for people with eczema . Accessed on 19/05/2020. Available from https://eczema.org/blog/advice-on-coronavirus-covid-19-for-people-with-eczema/

6. NIH National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf