City Research Online

City St George's, University of London

Citation: Harrold, K., Gould, D. J. & Drey, N. (2015). The management of cytotoxic chemotherapy extravasation: A systematic review of the literature to evaluate the evidence underpinning contemporary practice. European Journal of Cancer Care, 24(6), pp. 771-800. doi: 10.1111/ecc.12363

This is the accepted version of the paper.

This version of the publication may differ from the final published version. To cite this item please consult the publisher's version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/13830/

Link to published version: https://doi.org/10.1111/ecc.12363

Copyright and Reuse: Copyright and Moral Rights remain with the author(s) and/or copyright holders. Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, unless otherwise indicated, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. For full details of reuse please refer to City Research Online policy.

City Research Online: http://openaccess.city.ac.uk/ publications@citystgeorges.ac.uk

THE EXTRAVASATION OF CYTOTOXIC CHEMOTHERAPY: A SYSTEMATIC REVIEW OF THE LITERATURE TO ESTABLISH THE LEVEL OF EVIDENCE UNDERPINNING CONTEMPORARY PRACTICE AND REVEAL ANY STUDIES THAT EXPLORE THE PATIENT EXPERIENCE, OR EVALUATE OUTCOME FROM THE PATIENT'S PERSPECTIVE.

Background

Extravasation is defined as the inadvertent administration of cytotoxic chemotherapy drugs with the ability to cause severe tissue damage, tissue necrosis, blistering or sloughing, into the surrounding tissues rather than into the vascular pathway as intended (Allwood et al 2002, Dougherty and Lister 2008, RCN 2010).

Statistically the incidence of extravasation is low; with it estimated that 0.01% - 6.5% of all cytotoxic drug administrations' will result in an extravasation (Albanell and Baselga 2000, Schulmeister 2011). However Wengstrom (2008) suggests that when judged against the number of adverse events associated with chemotherapy, such as neutropenic sepsis, mucositis and gastrointestinal disturbances, the absolute number of extravasations becomes significant. The outcome of an ineffectively managed extravasation can be potentially devastating (Ener et al 2004, Arroyo et al 2010, Roe 2011, Schulmeister 2011) with long term consequences having the potential to be even more disabling for the patient than their primary disease (Gault 1993).

Whilst there is a clear consensus of opinion that the regular training and education of all staff involved in the administration of cytotoxic chemotherapy, supported by up to date institutional policies and procedures, is a key factor in the effective prevention of extravasation (EONS 2007, UKONS 2008, Dougherty 2010, Schulmeister 2011); it is also recognised that regardless of healthcare providers taking every precaution to prevent extravasation, and irrespective of the experience, skill and knowledge of the practitioner administering the cytotoxic chemotherapy, it will still occur (Dougherty 2010, Schulmeister 2011).

Despite this, opinion as to the most clinically effective management strategy remains contentious (Roe et al 2013). It is recognised that currently policies and procedures are largely empirical, based on historical practice within institutions, prior experience and observational data, on 'expert' opinion and from uncontrolled non randomised trials

(Mader et al 2011). As such there is variation in practice, with some clinicians favouring the use of antidotes (Schulmeister 2011, Perez Fidalgo et al 2012) and others favouring use of saline washout (Steiert et al 2011, Harrold et al 2013).

The Department of Health (DOH) is strongly committed to ensuring patients not only receive high quality care within an equitable service, but that the patient experience of the care provided also plays a significant part in the development of clinical practice guidelines. By making clinical practice more 'patient centred' taking into account their opinion of the care provided, this aims to improve quality, outcome and experience (DOH 2010b, 2011b, 2011c, 2012a) with Doyle et al (2013) establishing that in many circumstances, clinical effectiveness and outcome are directly linked to patient experience.

Objectives

To establish the level of evidence that underpins contemporary practice in the management of cytotoxic chemotherapy extravasation, the number of studies supporting each management strategy and to investigate the prevalence of studies exploring the patient experience or evaluating outcome from the patient's perspective.

Research questions

The questions this literature review addresses are:

- What level of evidence supports the use of antidotes in the management of cytotoxic chemotherapy drug extravasation?
- What level of evidence supports the use of saline wash out in the management cytotoxic chemotherapy drug extravasation?
- Is there any evidence to clearly show one technique as being more effective than the other?
- Are there any studies published that consider outcome from the patient's perspective?
- Are there any studies that explore the patient experience?

DRAFT

Method

Search process

A search of the literature was undertaken to source publications relating to extravasation management dating from the introduction of cytotoxic drugs as a cancer treatment in the 1960's to December 1st 2012. This was undertaken by accessing Pub-Med, Embase, Cinahl, Scopus, the British Nursing Index (BNI) and the Cochrane library for published clinical articles in professional and academic journals, including literature reviews, case studies and clinical trials, professional speciality text books, National and International Guidelines and pharmaceutical company literature. The United Kingdom national extravasation website was accessed; also a manual search of the bibliographies of associated articles and associated reference lists of the literature was carried out once sourced citations had been screened for eligibility. Details of the electronic search process can be found in Table 1.

Screening process

The identified literature was screened in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) four phase flow diagram (Moher et al 2009) and is presented in Table 2.

Inclusion criteria

Publications detailing non surgical management strategies in both the clinical and laboratory setting, which aimed to prevent ulceration or tissue necrosis following cytotoxic drug extravasation into the subcutaneous tissue of humans or animals. Both quantitative and qualitative studies were included with the purpose of identifying any studies which evaluated extravasation management from the patient's perspective. Language restrictions: Only papers written or translated into English.

Exclusion criteria

All citations detailing surgical intervention, the treatment of ulceration as a result of ineffective extravasation management, or relating to the prevention of skin ulceration following the topical application of cytotoxic drugs were excluded.

Also excluded were citations relating to the extravasation of contrast agents, analgesics, antibiotics, non chemotherapy vesicant drugs, liposomal cytotoxic drug preparations,

parenteral nutrition, anti-inflammatories, blood products or proteins and those relating to extravasation recall phenomenon, systemic toxicity from cytotoxic drug administration and records of dermatological toxicity from systemic therapies.

All citations relating to chemotherapy extravasation into the mediastinum or intrapleural extravasation were excluded, plus papers reviewing the incidence of extravasations or detailing its potential causes, extravasation prevention protocols or risk management strategies, extravasation detection criteria, reporting criteria and those discussing the physiology of tissue necrosis following drug extravasation.

Abstract review

Full texts were retrieved from the sourced citations if the abstract fulfilled the inclusion criteria and addressed one or more of the research questions. Full text papers were also retrieved if no abstract was available, but the title indicated that it fulfilled one or more of the above criteria.

Quality assessment and data extraction

Publications were appraised and graded using tools based on The Oxford Centre for Evidence Based Medicine's hierarchy of evidence levels (OCEBM 2011).

Final screening process and analysis

A Final analysis of the literature found there to be a significant lack of OCEBM level 1 systematic reviews. This outcome is supported by the findings of Gopalakrishnan et al (2012) who could find only case reports and case series describing successful outcomes with different interventions when attempting to undertake a Cochrane Review on the management of skin extravasation injury in neonates.

Similarly Drake (2012) carried out a short cut review to evaluate the evidence behind use of dexrazoxane following anthracycline extravasation. Despite identifying 211 relevant papers, none were RCT's and only one was considered eligible for evaluation being classified level 2c evidence (OCEBM 2009).

Whilst there were many articles reviewing the literature on extravasation management techniques, few of these gave any inclusion or exclusion criteria for the literature

reviewed or evidence how the literature was critically appraised, with the majority of recent publications being case reports, selective reviews or 'expert' opinion (EONS 2007, Schulmeister 2011a).

There were also numerous papers detailing single cases often with multiple management strategies used, making the results unreliable and inconclusive.

Taking these limitations into account, any paper graded OCEBM (2011) level 4 or above was included for evaluation within the final analysis of the literature within this review. Excluded were any, reviews based on 'expert' opinion or personal judgements and papers detailing single case reports. As a result, of the total one hundred and eighty nine papers initially identified, one hundred and three were excluded as being OCEBM (2011) level 5 evidence.

Of the remaining eighty six papers, thirty eight detailed animal studies. Whilst the use of controlled animal studies has historically been the basis for the evaluation of potential management strategies, the validity of using animal studies is limited in a number of ways. Firstly, animal skin differs anatomically to that of man (Dorr et al 1980), with differences in texture, elasticity and structure of the underlying dermal layers resulting in cytotoxic agents having to be injected intradermally as opposed to subcutaneously; Also, there is a major difference in the ulceration characteristics between the animals used (rats, pigs, guinea pigs and mice) possibly due to the difference in quantity of subcutaneous fat, which would again limit the applicability of these studies and contribute to the conflicting results. As a result of the anatomical difference between animal and man, the majority of animal studies administer the cytotoxic agent intradermally (a shallow injection just within the skin to form a superficial skin bubble) as opposed to subcutaneously (a deeper injection under the skin, into the subcutaneous tissue layer between skin and muscle) which would more closely mimic an inadvertent extravasation in clinical practice. It could therefore also be suggested that the resulting tissue damage from an intradermal extravasation would naturally vary to than from a subcutaneous extravasation.

It is also thought that the increased vasculature of rodent skin reduces the severity of ulceration (Kassner 2000), which would subsequently require the administration of a

higher drug concentration in order to more closely mimic a clinical injury. However evidence from early clinical trials show this not to be the case with many using administering ID anthracyclines at a concentration much lower than that used in clinical practice (Cohen 1979, Dorr et al 1980a, Laurie et al 1984). The most commonly used concentration in animal studies is 1mg/ml, a much lower concentration than the 2mg/ml which is used in clinical practice (eMC Doxorubicin Rapid Dissolution, point 6) and volume of drug infiltrated also appears to vary between species, ranging from 0.05 mls – 1ml.

Another limitation of animal studies is that they limit findings to purely clinical outcome as they are unable to evaluate outcome from the patient's perspective, to evaluate level of discomfort or the impact on activities of daily life. It therefore becomes very difficult to directly extrapolate the results from animal studies into clinical practice and consequently these studies were excluded from the final review.

The remaining forty eight papers were further appraised to exclude those that reported management of ulcerations, papers that could not be sourced but the abstract indicated unsuitability and text book chapters. This resulted in a total of twenty nine papers included in the final analysis of the evidence supporting current strategies cited for extravasation management. (Table 2.2)

Risk of bias

It is acknowledged that whilst every care has been taken to screen the literature in accordance with PRISMA guidelines and the Cochrane criteria for systematic reviews (Higgins and Green 2011) this process has been undertaken by a single individual and therefore bias can never be completely excluded.

Results

The objective of this literature review was to establish the level of evidence that underpins contemporary practice in the management of cytotoxic chemotherapy extravasation and the number of studies supporting each management strategy. It also aimed to investigate the prevalence of studies that explore the patient experience or evaluate outcome from the patient's perspective.

Level of evidence

There is a lack of clear cut scientific data with published work in this field focusing largely on case studies from institutions or from individuals reporting a single management strategy in order to validate their practice.

The majority (n=18) of the twenty nine papers reviewed were level 4 evidence and presented studies that utilised case series design (Figure 1).

Number of studies supporting each management strategy

Of the twenty nine papers included in the final data analysis, eighteen reported on the use of various antidotes (Figure 2).

Of interest; none of the thirty eight excluded animal studies evaluated the use of saline washout, all focused on the use of antidotes.

Is there any evidence to clearly show one technique as being more effective than the other?

No studies could be sourced that compared the use of strategies such as saline washout against the use of antidotes.

Are there any studies published that consider outcome from the patient's perspective?

No published studies could be sourced that explored outcome from the patient's perspective.

Are there any studies that explore the patient experience?

No studies could be sourced that evaluated the patient experience of extravasation management.

Discussion

Whilst 55% (n=103) of the initial retrieved citations (n=189) were level 5 evidence and therefore excluded from the final analysis, some have been used for discussion purposes (Perez-Fidalgo et al 2012, Wengstrom and Margulies 2008, EONS 2007, UKONS 2008).

DRAFT

The rationale for this being that contemporary practice appears to be guided by publications from national and international societies: the European Oncology Nursing Society (Perez-Fidalgo et al 2012, Wengstrom and Margulies 2008, EONS 2007), the European Society of Medical Oncology (Perez-Fidalgo et al 2012), and the United Kingdom Oncology Nursing Society (UKONS 2008) alongside 'expert opinion' from authors such as Langer (2000 a, b, 2001, 2006, 2007, 2008, 2009, 2010 a, b, 2012) Schulmeister (2005, 2007 a, b, c, d, e, 2008, 2009 a, b, 2010 a, b, c, 2011), Dougherty (2003, 2008, 2010, 2011) and Gault (1993, 1997). This would suggest that the management of extravasation continues to remain empirical and based on the expert views of lead opinion makers.

The lack of comparative studies between the two main strategies (saline washout or antidotes) is explicable due to difficulty ensuring their validity and reliability, the multiple extraneous variables and the ethical considerations making it unfeasible to use a control group. Also because in order for quantitative studies of this nature to yield statistically valid results, the sample size requirements would be too difficult to achieve due to the relatively small number and sporadic occurrence of extravasation. Consequently, in order to accurately control the multiple extraneous variables including age, sex, extravasated drug, site of extravasation, volume of extravasation, drug concentration, various co-morbidities, time to intervention, the minimum sample size requirement would be huge and consequently impossible to achieve without undertaking an international multi-centre study or collecting data over many years.

Whilst there is no clear evidence to suggest one management strategy is more effective than the other, all of the oncology societies (EONS, UKONS, ESMO) have published guidelines that favour the use of antidotes as opposed to saline washout. Perez Fidalgo et al (2012) stating that there is *'scarce experience'* in the use of saline washout technique (p71), EONS (2007) reporting that *'a saline flush out technique could also be used – but this approach requires specialist advice'* (p 23) and neither Wengstrom and Margulies (2008) or UKONS (2007) make any reference to the option of saline washout as a management strategy at all. This further upholds the opinion of Steiert et al (2011) that more evidence needs to be published supporting the use of saline washout technique as a valid alternative.

The main finding in this review, was the significant lack of published literature on the patient experience of extravasation management, with there being no published studies evaluating the quality of care in extravasation management, nor exploring aspects of care that are described as 'good' or 'bad' from the patients perspective, or detailing patient reported outcomes. The only outcome measure reported in the sourced literature was that the extravasation management strategy prevented any tissue necrosis that resulted in the need for surgical debridement or resection (Larson 1982, Bertelli 1994, Mourisden et al 2007, Steiert et al 2011).

Conclusions

Implications for practice and further research

Due to the obvious practical and ethical considerations in undertaking RCT's to validate extravasation management strategies, it is suggested that outcomes based research should underpin contemporary extravasation management guidelines and that all oncology units should monitor and report the outcome of their practice in order to validate the strategy used.

In considering National policy aimed at improving patient experience of NHS care (DOH 2010b, DOH 2012a) and the views of Doyle et al (2013) that patient experience and opinion of how well or badly health care interventions are managed directly impacts on their perception of its clinical effectiveness and outcome, the current lack of research into the patient experience of extravasation management is an area that needs to be addressed.

The majority of sourced papers in this literature review utilised case study methodology as a means of reporting and developing theory on the effectiveness of specific extravasation management strategies. It is suggested that further research should employ this methodology to explore the effectiveness of extravasation management strategies, as this would enable the patient experience to be contextualised in relation to both the clinical setting and the strategy used (saline washout or use of antidotes) and to reveal if these bear any relevance to patients perception of effectiveness and outcome.

DRAFT

Table 1
Electronic search process

Data base search & date	Search terms details	Number of citations retrieved
PubMed NCBI data base search last carried out on 20/05/2012 via http://www.ncbi.nlm.nih.gov/pubmed A 'My NCBI – what's new' weekly alert was also established to source new publications as they appeared. This was enabled via the PubMed National Centre for Biotechnology Information at the U.S. National Library of Medicine.	'Chemotherapy extravasation', 'extravasation management', 'cytotoxic drug extravasation' 'cytotoxic extravasation injury' Search details: Chemotherapy: ("drug therapy"[Subheading] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "chemotherapy"[All Fields] OR "drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "chemotherapy"[All Fields]) AND extravasation [All Fields] Extravasation [All Fields] AND ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields])	These searches resulted in the retrieval of 2640, 936, 91 and 66 citations respectively.
A Scopus document search was last carried out on 20/05/2012 by accessing the database at http://www.scopus.com/home.url	A 'title / abstract / keywords' search with the search terms: 'Management of extravasation AND chemotherapy' was used	This search identified 125 citations.
The Cochrane database of systematic reviews was last accessed on 25/05/2012 via its website http://www.thecochranelibrary.com	A 'title / abstract / keywords' search with the search term of 'cytotoxic drug extravasation' By broadening the search term to 'extravasation'	No results found 2 citations were retrieved from the database's 7272 records.
The Embase, Cinahl data base was last accessed on 20/05/2012 via http://www.library.nhs.uk/mylibrary	Search terms 'chemotherapy AND extravasation AND cytotoxic AND drug OR extravasation AND management'	resulted in 1090 and 347 results respectively
The British Nursing Index (BNI) was last accessed on 27/05/2012 via the RCN website at http://www.rcn.org.uk/development/library/elibrary	Search terms 'chemotherapy extravasation' and 'extravasation'	Resulted in 17 and 39 citations respectively.
www.extravasation.org last accessed on 07/01/2012		Identified 98 citations on the websites reference list.

DRAFT

Table 2

Screening of the Literature

Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 www.prisma-statement.org.

	Records Identified through database searching	**Additional records identified through other sources**	**Total number of texts initially identified**
1. Identification of the literature	PubMed NCBI data base searches were last carried out on 20/05/2012 via http://www.ncbi.nlm.nih.gov/pubmed using the search terms: 'Chemotherapy extravasation', 'extravasation management', 'cytotoxic drug extravasation' 'cytotoxic extravasation injury'. resulting in the retrieval of 2640, 936, 91 and 66 citations respectively A Scopus document search was last carried out on 20/05/2012 by accessing the database at http://www.scopus.com/home.url A 'title / abstract / keywords' search with the search terms: 'Management of extravasation AND chemotherapy' was used and this search identified 125 citations. The Embase, Cinahl data base was last accessed on 20/05/2012 via http://www.library.nhs.uk/mylibrary using the search terms 'chemotherapy AND extravasation AND cytotoxic AND drug OR extravasation AND management' resulting in 1090 and 347 results respectively. The British Nursing Index (BNI) was last accessed on 27/05/2012 via the RCN website at http://www.rcn.org.uk/development/library/elibrary using the search terms 'chemotherapy extravasation' with a resulting 17 citations sourced and 'extravasation' which resulted in 56 citations The Cochrane database of systematic reviews was last accessed on 25/05/2012 via its website http://www.thecochranelibrary.com and a 'title / abstract / keywords' search with the search term of 'cytotoxic drug extravasation' produced no results. By broadening the search term to 'extravasation' 2 citations were retrieved from the database's 7272 records.	A search was also undertaken by accessing www.extravasation.org on 07/01/2012 which identified 98 citations on the websites reference list. A further 71 sources were added during the search for full texts and following a hand search through the bibliographies of retrieved texts.	**5,539** texts originally identified.

DRAFT

	Removal of duplicates and sources not published in English	Records to be screened	Indexed texts
2. Screening process **i. Language and relevance** **ii. Duplicates**	Following screening for language and relevance of the 3733 PubMed sourced citations these were combined into an alphabetical PubMed bibliography by author, so allowing for duplicates to be identified and removed. This resulted in 297 PubMed citations saved prior to assessment of eligibility for inclusion in the final data synthesis. Of the 125 Scopus results 43 were saved following screening as detailed above. The Embase, Cinahl citations combined, filtered for duplicates and further filtered for citations not published in English resulted in 271 citations saved for eligibility screen. The citations accessed from the BNI were filtered for duplicates and sources not directly translated into English resulting in 54 citations. Of the 2 results sourced from the Cochrane library, only one related to intravenous extravasation management and was saved for further eligibility review.	All sources were then amalgamated and further filtered for duplicates. This resulted in **351** citations indexed for eligibility screening.	**351** Texts to be screened for eligibility
	Full text excluded	**Texts unable to be obtained**	**Full text assessed for eligibility**
3. Eligibility **Exclusion and inclusion criteria as specified in main text**	Using the specified criteria as described 141texts were excluded as not relevant to the literature review.	A further **31** texts could not be sourced from Med-line, Cinahl, the RCN database, Scopus or via the post graduate library services and were excluded on the basis of the abstract or title. Of the final 189 texts identified for inclusion review 23 were unable to be sourced (December 2012).	**179** texts were initially included for as eligible for review. A further 10 texts were sourced through data base alerts and ongoing bibliography searches.
	Literature included in final review	**Literature excluded from final review**	**Total to be included in final analysis**
4. Included texts	Eligibility criteria for papers included in the final data analysis was any paper OCEBM Level 4 and above	Excluded were all animal studies irrespective of OCEBM grading, non systematic reviews, reviews based on expert opinion or personal judgements and papers detailing single case reports as these were all graded level 5 based on OCEBM (2011) criteria.	**29 texts** identified as eligible for inclusion in the final analysis

DRAFT

Figure 1: Levels of evidence

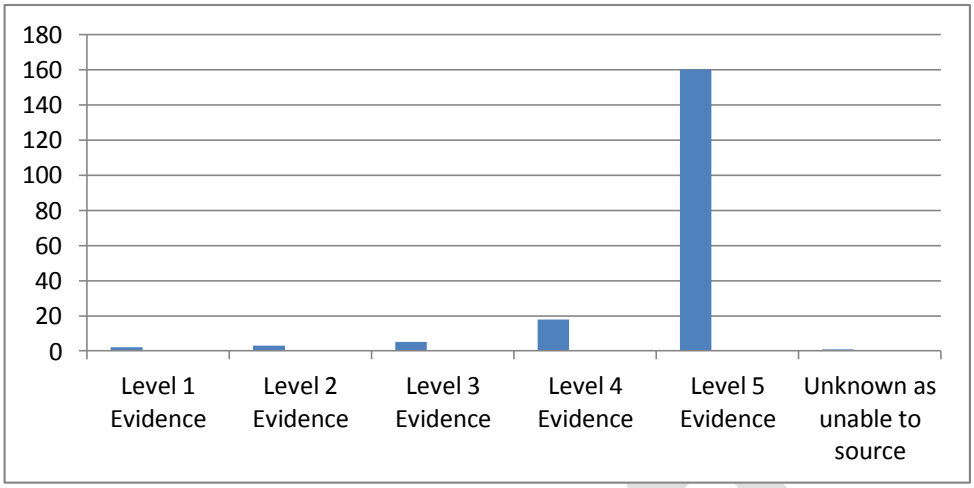

Figure 2: Number of papers sourced reporting an individual strategy

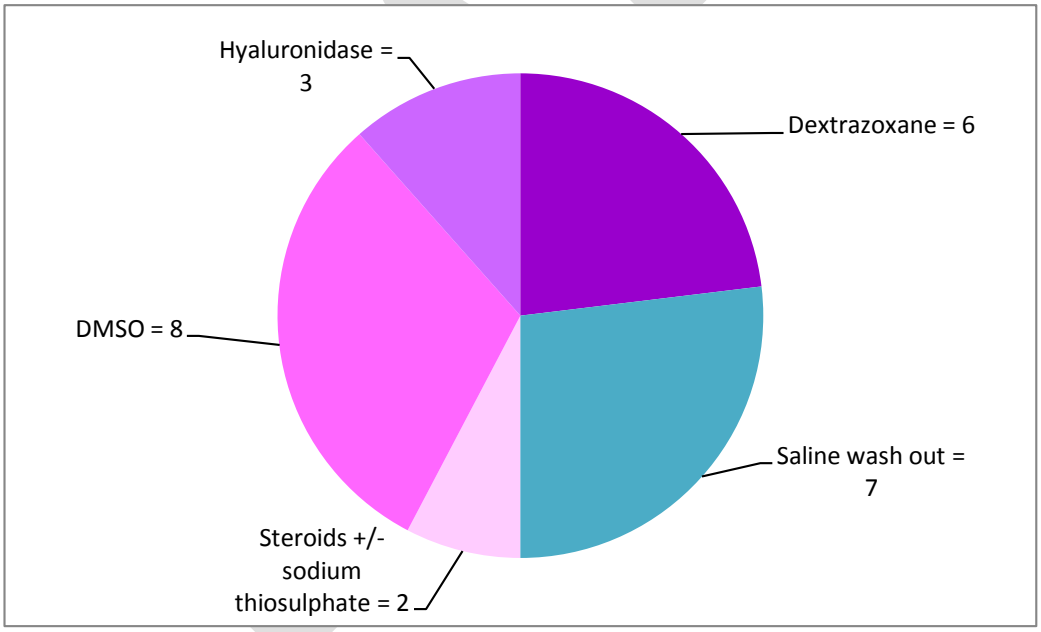

Table 3: Literature included in the final analysis

WATCH AND WAIT / ICE AND ELEVATE / CONSERVATIVE MEASURES					
Date of publication	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
1982	Larson DL. Treatment of tissue extravasation by antitumor agents. Cancer. 1982 May 1; 49(9):1796-9.	The application of ice inactivates the locally destructive effects of doxorubicin.	**Design** Case series report detailing the immediate treatment of 50 extravasations occurring over a 20 month period **Intervention** ICE AND ELEVATE.	Report on 50 patients treated over a 20 month period using 'watch and wait' **OCEBM Level 4**	**First example of vasoconstriction as a management technique cites recent studies personally communicated by Dorr as evidence** 1. Clearly focused research question To find a simple and predictable management strategy as use of antidotes remains theoretical and unpredictable. Use of immediate surgery is again anecdotal and unproven. 2. The method used was a detailed review of all cases of extravasation (n=50) within a 20 month period, which was appropriate to answer the question posed. 3. No explicit detail of the 50 cases – just says 50 patients receiving doxorubicin or Vincristine. 4 – 7. No detail of any of the extravasation injuries, no outcomes, no confounders Presents only one case study out of 50 Patients seen by plastic surgeon within 72 hours. If no further deterioration over 10 days then usually ok, if pain then usually go on to require surgical excision. States that only 12 of the 50 patients seen required surgery (less than 1/3). Quoted by Schulmeister 2007 stating 1/3 of patients went on to require surgery. Not precise, no measurable evidence States the main indication to proceed to surgery is pain and convincing the patient to the risk of infection Impossible to evaluate the results In the methods section it states that no drugs are given locally, but in the single case report it states that the patient was given 50mg s/c prednisolone.

DRAFT

Date	Reference	Hypothesis / aim	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
1985	Larson DL. What is the appropriate management of tissue extravasation by antitumor agents? Plast Reconstr Surg. 1985 Mar; 75(3):397-405.	Considers pain, usually associated with varying degrees of skin involvement, to be the only indication for surgery Advocates ice and elevate	**Design** Case series reports **Intervention** ICE and ELEVATE	Data collected on 175 patients **OCEBM – Level 4 – case series as no follow up**	**Seminal article widely quoted as the largest clinical study on extravasation to date (according to Kennedy 2003)** 1. Does have a clearly defined research question 2. Method used to answer the question was appropriate 3. Representative cohort of patients – all who attended with extravasation injuries 4.No detail of type of drug involved in extravasation – general overview in table with no figures 5. Objective measurement of outcome – either did or didn't require surgery 6.No consideration of confounding factors – size of extravasation, type of drug, time to treatment etc 7 No definitive follow up period Results Most of the paper is discussion about alternative options that have been proposed in the literature States that up to 1984 no less than 15 antidotes have been investigated in animal studies, but that they report a small number of cases treated in a variety of ways No clear detail. States that 89% patients responded to ice and elevate Supports his previous publication of case reports in 1982 Reports on 4 cases of vinca alkaloids that required excision and grafting
2002	Langstein HN, Duman H, Seelig D, Butler CE, Evans GR. Retrospective study of the management of chemotherapeutic extravasation injury. Ann Plast Surg 2002 Oct;49(4): 369-74	Most cases of extravasation can be managed conservatively, with directed surgical treatment of the ulceration when appropriate	**Design** Retrospective Case Series Analysis **Intervention** Conservative - Watch and wait	44 cases over 6 years **OCEBM – Level 4**	Retrospective study Advocates 'watch and wait' conservative treatment, followed by surgical debridement if deemed necessary, Paclitaxel and doxorubicin were the 2 most common drugs Only 26 of 42 patients required plastics referral and only 10 of the 26 required surgical intervention / debridement Mean time of injury to referral was 40 days Approx 25% of patients requiring surgery In 2 patients, partial skin graft loss developed and secondary epithelialisation caused slight limitations in range of motion. One patient who was treated with incision and drainage died of fungal sepsis.

DRAFT

SUBCUTANEOUS OR TOPICAL CORTICOSTEROIDS +/- SODIUM THIOSULPHATE					
Date	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
1979	Barlock AL, Howser DM, Hubbard SM. Nursing management of adriamycin extravasation. Am J Nurs. 1979 Jan; 79(1):94-6.	Corticosteroids will reduce the severe inflammatory response from doxorubicin extravasation.	**Design** Prospective randomised study with all patients given doxorubicin included **Intervention** S/C HYDROCORTISONE SODIUM SUCCINATE FOLLOWED BY TOPICAL HYDROCORTISONE CREAM, ICE AND ELEVATE	Small sample size n=9 **OCEBM Level 2 graded down to Level 3** (no control arm and very small study size)	**P – 139 included, but only 9 evaluated as extravasations** **I -** Group A – IV hydrocortisone sodium succinate (via cannula used to administer chemo) followed by topical ice pack x 5 pts. **I -** Group B – Cannula removed and hydrocortisone sodium succinate given ID and S/C by multiple inj around the extravasation site x 4 pts. Then – 1% hydrocortisone cream applied and area covered with gauze **C –** No control arm **O -** Neither group went on to develop skin necrosis or ulcers but those in group A did have pain and erythema, with loss of patency in the vein. **Appraisal** **R –** No detail of how subjects were randomised No reference to variables **A –** Some patients had additional steroids **M –** not blinded Randomised trial, but no control arm No indication of how patients were randomised to arm A or B. No control group Still = pain at site requiring analgesia Unknown volume or size of extravasation Valid as a general discussion only.
1992	Tsavaris NB, Komitsopoulou P, Karagiaouris P, Loukatou P, Tzannou I, Mylonakis N, Kosmidis P. Prevention of tissue necrosis due to accidental extravasation of cytostatic drugs by a conservative approach. Cancer Chemother Pharmacol. 1992; 30(4):330-3.	**Aim:** To evaluate comparatively the effectiveness of a conservative approach to treatment, using two therapeutic schedules (with and without sodium thiosulfate	**Design** Case control - Comparative Study **Intervention** HYDROCORTISONE AND DEXAMETHASONE vs SODIUM THIOSULPHATE plus HYDROCORTISONE AND DEXAMETHASONE	63 patients **OCEBM – Level 3**	**1.** Clearly focused issue 2. Appropriate method used to answer the question 3.Clearly defined recruitment process with eligibility criteria No power calculation and no explanation of time frame (5 years) 4. doesn't specify how group A or group B were chosen 5. Measurement of outcome was objective and by specified methods 6. No consideration of any confounders - Various extravasated drugs – all vesicants **7. Outcome** The mean healing time for group B, which received ST was about half that for group A, which did not. – Concluded the application of conservative measures during chemotherapy may prevent tissue necrosis that Low precision of results

DRAFT

DMSO					
Date	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
1983	Olver IN, Schwarz MMA. Use of dimethyl sulfoxide in limiting tissue damage caused by extravasation of doxorubicin. Cancer Treat Rep. 1983 Apr; 67(4):407-8.	DMSO as an anti-inflammatory free radical scavenger will help promote healing..	**Design** Case reports **Intervention** DMSO for Doxorubicin extravasations However also used ice and also used sodium bicarbonate	3 case reports **OCEBM – Level 4**	Limited detail Mixed management strategy Outcome measured at different time frame Not true case studies Inconclusive
1987	Ludwig CU, Stoll HR, Obrist R, Obrecht JP. Prevention of cytotoxic drug induced skin ulcers with dimethyl sulfoxide (DMSO) and alpha-tocopherole. Eur J Cancer Clin Oncol. 1987 Mar; 23(3):327-9.	Both DMSO and alpha-tocopherol (vitamin E) are free radical scavengers. DMSO is an anti-inflammatory free radical scavenger that is purported to help promote healing, whilst vitamin E is thought to protect against highly reactive radicals.	**Design** Clinical pilot study using case series methodology **Intervention** DMSO and ALPHA-TOCOPHEROLE Topically for anthracyclines and Mitomycin extravasations	Small sample size (n = 8) **OCEBM Level 4**	**1.** Clinical pilot study to evaluate the effectiveness of DMSO and a-tocopherol for doxorubicin or mitomycin extravasation 2. Case series is the most appropriate way to address the problem due to the sporadic and low incidence rate 3. All patients that presented with a extravasation during an explicit time period were recruited Specific inclusion criteria 4. Allowed for adequate follow up – until resolution of symptoms Not possible to eliminate all extraneous variables due to limited number included in study, however the patient group is a proper reflection of those in clinical practice and the drug concentrations are standard for clinical practice (2mg / ml) Positive results
1988	Olver IN, Aisner J, Hament A, Buchanan L, Bishop JF, Kaplan RS. A prospective study of topical dimethyl sulfoxide for treating anthracycline extravasation. J Clin Oncol. 1988 Nov; 6(11):1732-5.	DMSO is an anti-inflammatory free radical scavenger that is purported to help promote healing	**Design** Single arm study (pilot study) **Intervention** DMSO 6 hourly x 14 days	20 patients recruited in a prospective study **OCEBM – Level 3**	**P-** 20 patients recruited in a prospective study **I-** DMSO for anthracycline extravasation **C-** No control group – would have been unethical **O-** Effective antidote **R-** No randomisation – all included **A-** All treated equally and all accounted for **M-**All observed for 3 months apart from 2 who died and 2 who were lost to follow up **Outcome** Clearly focused question with outcome objectively measured. No patients progressed to ulceration or required surgical intervention Valid results

DRAFT

Date of publication	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
1989	Lawrence HJ, Walsh D, Zapotowski KA, Denham A, Goodnight SH, Gandara DR. Topical dimethylsulfoxide may prevent tissue damage from anthracycline extravasation. Cancer Chemother Pharmacol. 1989; 23(5):316-8.	DMSO is an anti-inflammatory free radical scavenger that is purported to help promote healing	**Design** Prospective case series **Intervention** ICE, LOCAL GLUCOCORTICOID INJECTION, AND DIMETHYLSULFOXIDE (DMSO) 55%-99% applied topically every 2-4 h after extravasation for a minimum of 3 days	case series reports of 4 patients **OCEBM – Level 4**	1. Aimed to report on the efficacy of DMSO in preventing tissue necrosis following anthracycline extravasation 2.Case series is appropriate for non animal studies 3. 4 consecutive cases of anthracycline extravasation 4. No control arm Limited validity in supporting use of DMSO due to mixed management strategy therefore could dispute the effect, plus no specifics given as to length of follow up and no confounding factors accounted for
1994	St Germain B, Houlihan N, D'Amato S. Dimethyl sulfoxide therapy in the treatment of vesicant extravasation: two case presentations. J Intraven Nurs. 1994 Sep-Oct;17(5):261-6.	Free radical scavenger	**Design** case studies **Intervention** DMSO	Only 2 Patients **OCEBM – Level 4/5**	Very small sample size Limited validity
1995	Bertelli G, Gozza A, Forno G, Vidili M, Silvestro S, Venturini M, Del Mastro L, Garrone O, Rosso R, Dini D. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. J Clin Oncol. 1995 Nov; 3(11):2851-5.	Aim: To evaluate the activity and tolerability of dimethylsulfoxide (DMSO) a free radical scavenger in the prevention of soft tissue toxicity after extravasation of cytotoxic drugs	**Design** Open Prospective Study using case series methodology **Intervention** DMSO	144 patients with extravasations 127 entered in study doxorubicin (n = 11) epirubicin (n = 46) mitomycin (n = 5) mitoxantrone (n = 13) Cisplatin (n = 44) Carboplatin (n = 6) ifosphamide (n = 14) fluorouracil (n = 5) **OCEBM – Level 3**	Topical 99% DMSO applied Only one patient ulcerated Multiple drugs therefore many variables not accounted for Cited by Langer et al 2000b as being limited in design as the study had no control arm (however as this was a clinical study having a control arm would have been unethical!) Appears to show valid results

DRAFT

Date of publication	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
1996	Bonnetblanc JM, Bordessoule D, Fayol J, Amici JM. Treatment of accidental extravasation of antitumor agents with dimethylsulfoxide and alpha-tocopherol. Ann Dermatol Venereol. 1996; 123 (10):640-3.	**Hypothesis** Free radical scavenger	**Design** Open prospective study using case series methodology **Intervention** DMSO and A-Tocopherol	10 patients **OCEBM - Level 4**	Absence of secondary ulcerations and the preservation of the implant sites Doesn't specify nature of extravasated drugs in the abstract positive results
2004	DeLemos M.L. Role of Dimethylsulphoxide for management of chemotherapy extravasation. J Oncol Pharm Pract December 2004 vol. 10 no. 4 197-200	Extravasation of anthracyclines is a rare complication that can lead to severe tissue necrosis and ulceration. With conservative measures (e.g., limb elevation, cooling), ulceration may develop in 28% of patients. Topical dimethylsulfoxide is commonly suggested as an antidote. However, there are inconsistent and sometimes conflicting animal data on its efficacy and safety	**Design** Review based on 2 clinical studies (n=147) following a database search with explicit criteria **Intervention** DMSO	147 patients **Presented as a review, but not upheld by OCEBM Appraisal criteria as level 1therefore graded as level 2**	Doesn't give a focused research question 'The following review will assess the clinical evidence on the use of DMSO' **F** = Search Strategy: Ovid Medline (1966 to April 2004) was searched using the medical subject headings of 'Dimethyl Sulphoxide' and 'Extravasation of Diagnostic and Therapeutic Materials', and limited to English language and human articles. No 'results' section No outline of the number of titles and abstracts reviewed, the number of full-text studies retrieved, or the number of studies excluded together with the reasons for exclusion. **A** No inclusion or exclusion criteria **A** Inclusion criteria appears to be papers with more than 10 patients in the study Only two case series included more than 10 patients Results presented as a table Indicates DMSO to be a well tolerated effective management strategy to prevent ulceration

DRAFT

HYALURONIDASE					
Date	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
1994	Bertelli G, Dini D, Forno GB, Gozza A, Silvestro S, Venturini M, Rosso R, Pronzato P. Hyaluronidase as an antidote to extravasation of Vinca alkaloids: clinical results. J Cancer Res Clin Oncol. 1994;120(8):505-6.	Hyaluronidase will aid reabsorbtion	**Design** Case series (prospective) **Intervention** HYALLURONIDASE FOR VINCA'S	7 patients **OCEBM - Level 4**	A. Appropriate method for the question asked All cases of vinca alkaloid extravasation recruited, but no explanation of time frame or sample size No control as unethical Subjective measurement / very vague No confounders accounted for – dose, volume, drug etc B **Positive results but small sample size** Follow up time – not specific C. Outcome – favourable
1996	Du Bois, A., Fehr, M. K., Bochtler, H., & Koechli, O. R. (1996). Clinical course and management of paclitaxel extravasation. Oncology Reports, 3(5), 973-974.	Hyaluronidase will aid reabsorbtion of the extravasated drug	**Design** Case control study **Intervention** APPLICATION OF ICE +/- HYALURONIDASE for paclitaxel extravasation	4 cases **OCEBM - Level 4**	Small sample size therefore limited validity Negative results Found that hyaluronidase increased the time to healing
1997	Bertelli G, Cafferata MA, Ardizzoni A, Gozza A, Rosso R, Dini D, Dorr RT. Skin ulceration potential of Paclitaxel in a mouse skin model in vivo. Cancer June 1, 1997; 79 (11): 2266-68	Hypothesised that if hyaluronidase was shown beneficial in a mouse skin model this should translate into clinical practice	**Design** case series - correspondence **Intervention** HYALURONIDASE	7 patients - 5 x paclitaxel - 2 x docetaxel **OCEBM – Level 4/5**	**A** Clearly focused issue Describes clinical data gathered on 7 patients Clinical observation - Appropriate method to appraise outcome in clinical practice Recruited as the event occurred dependant on extravasated drug 7 patients - 5 x paclitaxel - 2 x docetaxel Confounders not taken into consideration Unsuitable for control arm - unethical B **Positive results** Agrees with Dorr on use of hyaluronidase as an antidote. Followed up for 21 weeks C Clinically relevant, but small sample size and just correspondence as opposed to a reported clinical study

DRAFT

DEXRAZOXANE					
Date	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
2006	Frost A, Gmehling D, Azemar M, Unger C, Mross K. Treatment of anthracycline extravasation with dexrazoxane -- clinical experience. Onkologie. 2006 Jul; 29(7):314-8. Epub 2006 Jul 3.	To demonstrate that the treatment of anthracycline extravasation with dexrazoxane is potentially useful and safe.	**Design** Case reports **Intervention** DEXRAZOXANE	3 CASE REPORTS 3 cases of extravasation with 3 different anthracyclines. 2 pts treated with dexrazoxane **OCEBM – Level 4**	**Positive results – no surgery,** but the small sample size limits validity of results
2007	Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, de Wit M, Knoblauch P, Rasmussen A, Dahlstrøm K, Jensen PB, Giaccone G. Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. Ann Oncol. 2007 Mar; 18(3):546-50. Epub 2006 Dec 21.	**Aim:**To assess the efficacy and tolerability of dexrazoxane as an acute antidote in biopsy-verified anthracycline extravasation.	**Design** Two prospective, open-label, single-arm, multicentre studies **Intervention** DEXRAZOXANE	**Study 1** = 18 patients assessed for efficacy and 23 for safety **Study 2** = 36 for efficacy and 57 for safety **Total** = 53 patients **OCEBM - Level 2 / 3**	**P- Study 1** = 18 patients assessed for efficacy and 23 for safety **Study 2** = 36 for efficacy and 57 for safety **I-** Use of dexrazoxane for anthracycline extravasation **C-** no control group for comparison, the results were judged against 'standard practice' supposed to be surgery = historical control **O-** prevention of surgical debridement in all but one patient of the total 53 assessed However there were also grad 2-4 lab based toxicities = myelosuppression and raised liver enzymes **R-** no randomisation = cohort study **A-** all patients accounted for **M-** debatable as to the objectivity of measurements. No strict reporting criteria, clinical evaluation was vague. Subjective in reporting adverse events **Outcome** 53 patients all treated within 6 hours Extravasation verified by biopsy Only **1 required surgical intervention** **= positive outcome with valid results**
2008	Hasinoff BB. The use of dexrazoxane for the prevention of anthracycline extravasation injury. Expert Opin Investig Drugs. 2008 Feb; 17(2):217-23.	Aim: to evaluate the preclinical and clinical literature on the use of dexrazoxane in preventing anthracycline-induced extravasation injury.	**Design** Review **Intervention** DEXRAZOXANE	OCEBM Level	

DRAFT

Date of publication	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
2008	Langer SW. Treatment of anthracycline extravasation from centrally inserted venous catheters. Oncol Rev 2008; 2:114-116	**Aim:** To present data on 7 cases of Savene treatment of anthracycline extravasations from central venous catheters.	**Design** Case series methodology **Intervention** DEXRAZOXANE	7 x Cases **OCEBM – Level 4**	Clearly addressed issue Appropriate method to answer the question Uses 4 cases of CVC extravasation as detailed in the prospective studies reported by Mourisden et al (2007) of which Langer was a co-author and 3 from the literature Gives no indication of how the 3 cases were sourced No inclusion / exclusion criteria for searching the literature = **potential for selection bias** Limits validity of results **Positive outcomes** but... However the report does include 1 patient who went on to experience tissue necrosis at extravasation site
2011	Fontaine C, Noens L, Pierre P, DeGreve J Savene (Dexrazoxane) Use in Clinical Practice Support Care Cancer. Short communication. Published on line Springer-Verlag DO1 10.1007/s00520-012-1382-2 27/01/2012	Aim: To assess, in clinical practice, the efficacy and safety profile of Savene® for ACEV in different Belgian hospitals	**Design** Survey methodology using a retrospective questionnaires **Intervention** DEXRAZOXANE	Questionnaire sent to 44 hospitals resulting in data on 41 patients **OCEBM – Level 4**	**P –** 41 patients identified and included in results 28 had extravasation of an anthracycline from a CVC **I –** All treated with dexrazoxane **C -** Historically controlled study with need for surgical debridement as the 'control' **O –** generally positive outcome **R –** No randomisation as historical data from questionnaires **A –** Both peripheral and CVC extravasations , all treated equally **M –** Retrospective questionnaire, but limitations acknowledged **Outcome** In **two patients, surgical debridement was unavoidable due to extensive infiltration** of anthracyclines in the surrounding tissue. The scheduling of the planned chemotherapy courses could be maintained in 30 of 41 patients (73%). **Eight adverse events of haematological toxicity** **One Wound infection** Surgical intervention avoided in 92.9% cases Valid results

DRAFT

Date	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
2012	Drake D. Emergency Management of Anthracycline Extravasation. Emerg Med J September 2012; 29 (9): 777 – 779 Downloaded from emj.bmj.com on August 26, 2012 - Published by group.bmj.com	**Aim:** To establish whether intravenous dexrazoxane reduces the risk of tissue necrosis after extravasation of the chemotherapy agent anthracycline.	**Design** Short cut review **Intervention** DEXRAZOXANE	**OCEBM Level 1**	**Clearly defined research question** In (an adult presenting with peripheral anthracycline extravasation) will (treatment with intravenous dexrazoxane reduce the risk of soft tissue necrosis)? **Clearly defined search strategy** **No specific inclusion / exclusion criteria** However appears to be only papers graded 2 or above as the article by Mourisden (2007) was the only one included as all of the others were below level 2 Graded it a level 2c and from this **one study** deduced that there was promising evidence for dexrazoxane use

DRAFT

SALINE WASHOUT					
Date	**Reference**	**Hypothesis / aim of study**	**Study design / intervention**	**Sample size and level of evidence** (OCEBM 2011)	**Main Findings** (Appraised using PICO or CASP dependant on study design)
1993	Gault D.T Extravasation Injuries British Journal of Plastic Surgery. 1993; 46: p91-96	Rather than leave potentially harmful drugs to remain in the subcutaneous and perivenous space it is suggested preferable to physically remove the drug by flushing the area through with sterile saline 0.9%.	**Design** Retrospective case series review **Intervention** SALINE WASHOUT	96 patients **OCEBM – Level 4**	1. Doesn't ask a question, but presents alternative techniques for extravasation management 2.Recruited all patients who experienced an extravasation 3. Varying drugs, not all cytotoxics, no confounding factors taken into account 4. outcome appraised on need for further surgical intervention 5. assessment made on the 44 patients referred early 37 patients had saline washout alone 6. No explanation of why some had liposuction, some had SWOT and some had both **Outcome -** of the 44 patients treated with SWOT 39 had no further tissue damage (88.5%) the other 5 had minor skin blistering or delayed healing. None required surgical debridement Doesn't state how many of these patients had anthracycline extravasations **positive results as no surgery required** Not very precise results but still significant
1994	Scuderi N, Onesti MG. Antitumor agents: extravasation, management, and surgical treatment. Ann Plast Surg. 1994 Jan;32(1):39-44	Saline will wash the drug out of the tissues and steroids to reduce inflammation .	**Design** Cohort study **Intervention** EARLY SURGERY SALINE INJECTED AT SITE 20-90mls PLUS CORTICOSTEROIDS	40 patients **OCEBM – Level 3 / 4**	Appropriate method for the question asked 40 patients out of 52 referred – reason as to why only these 40 were chosen is cited as tumour type and extravasated drug. 3 patients excluded from results as late presentation (2 weeks post extravasation) Injected with s/c saline volume dependant on site No control group (but this would have been unethical) B. Superficial ulceration cleared within 10-14 days and no residual injury in any patient. All were followed up for between 6-18 months Takes no account of confounders ie those also treated with topical steroids Varying number of treatments with s/c saline from 3 – 6 applications – no rationale given as to why C. Outcome = 3 of 26 pts required surgery for deep tissue damage very vague descriptors, how outcome was measured etc
2000	Cicchetti S, Jemec B, Gault DT. Two case reports of vinorelbine extravasation: management and review of the literature. Tumori. 2000 Jul-Aug; 86(4):289-92.	**Hypothesis** Hyaluronidase to open up connective tissue followed by saline to wash the drug from the tissue	**Design** Case Reports **Intervention** HYALURONIDASE AND SALINE WASHOUT	2 Patients **OCEBM – Level 4**	Reports positive results with no surgery required

DRAFT

Date	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
2002	Khan MS, Holmes JD. Reducing the morbidity from extravasation injuries. Ann Plast Surg. 2002 Jun; 48(6):628-32; discussion 632.	**Hypothesis** Based on Gault's flushout hypothesis	**Design** Case Series **Intervention** SALINE WASHOUT	18 Patients **OCEBM – Level 3/4**	1. Clearly focused issue = reducing morbidity from an extravasation injury 2. Case series is the most appropriate means of addressing this issue in clinical practice 3. recruited within a specific time frame = 18 over 2 years from 97-99 4/5 All extravasations included. Not enough detail about outcome measures therefore allowing for bias, subjective No control arm 6. Seven extravasations were anthracyclines (1/3rd) 7. 6 month follow up 8 / 9 However 17 of the 18 patients had no untoward sequalae and the 1 patient who required surgical intervention was not treated within the protocol. Followed up for 6 months Intervention based on Gault's flushout technique Valid results
2005	Napoli P, Corradino B, Badalamenti G, Tripoli M, Vieni S, Furfaro MF, Cordova A, Moschella F. Surgical treatment of extravasation injuries. J Surg Oncol. 2005 Sep 15; 91(4):264-8; discussion 268-9.	**Aim:** The authors present their experience of treating anti-cancer drug extravasation by means of a composite surgical technique that consists of infiltration with physiological solution and hyaluronidase and subsequent manual aspiration of solutes alternated with profuse irrigation of the infiltrated area.	**Design** Report **Intervention** SALINE INFILTRATION, LIPOSUCTION AND WASHOUTWASHOUT	25 Patients **OCEBM – Level 4 / 5**	Explains the procedure of saline infiltration, liposuction and then washout, but gives no specific detail on individual patients, nature of the extravasated drug or specific measurement of outcome States that since the year 2000 this technique has been used on 25 patients of the 25 patients treated none had any ulceration or soft tissue damage
2011	Steiert A, Hille U, Burke W, Gohritz A, Zilz S, Herold C, Vogt PM. Subcutaneous wash-out procedure (SWOP) for the treatment of chemotherapeutic extravasations. J Plast Reconstr Aesthet Surg. 2011 Feb;64(2):240-7. Epub 2010 Jun 9.	**Hypothesis / Abstract** Report on a therapeutic approach using saline washout procedure without the application of specific antidotes. Advocates that based on the absence of comparative studies with regard to the efficacy of conservative therapy, SWOP should be offered as a therapeutic option for chemotherapeutic extravasations.	**Design** Prospective case series **Intervention** SALINE WASHOUT	13 patients **OCEBM – Level 4**	**P-** 13 patients **I-** Saline washout **C-** historical control of surgery **O-** none of the patients required surgery **R-**no randomisation or control arm – all extravasations included Multiple different drugs **A-** varying volumes of saline used dependant on volume of extravasate, All accounted for **M-** objective measures as in not requiring washout, but subjective in measurement of skin induration or other sequalae Outcome = positive Includes CVAD extravasations Cites Gault 1993 but has changed the procedure slightly Backs up MVCC rationale for treating category 1-3 extravasations with SWOP Say it can potentially be used 72hrs post extravasation 13 patients, 3 month follow up, Focused on outcome

DRAFT

Date	Reference	Hypothesis / aim of study	Study design / intervention	Sample size and level of evidence (OCEBM 2011)	Main Findings (Appraised using PICO or CASP dependant on study design)
2012	Gopalakrishnan PN, Goel N, Banerjee S. Saline irrigation for the management of skin extravasation injury in neonates. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008404. DOI: 10.1002/14651858.CD008404.pub2 Copyright © 2012 The Cochrane Collaboration. Published by JohnWiley & Sons, Ltd.	**Aim:** To determine the efficacy and safety of saline irrigation or saline irrigation with prior hyaluronidase infiltration on tissue healing in neonates with extravasation injury when compared to no intervention or normal wound care.	**Design** Systematic review of the literature Cochrane review **Intervention** SALINE IRRIGATION	**OCEBM –Level 1** **Cochrane review**	**Clearly defined research question** **Clearly defined search strategy** SELECTION CRITERIA: Randomised controlled trials (RCT) and quasi-randomised controlled trials comparing saline irrigation with or without hyaluronidase infiltration with no intervention or normal wound care in the management of extravasation injury in neonates. DATA COLLECTION AND ANALYSIS: three review authors independently reviewed and identified articles for possible inclusion in this review. MAIN RESULTS: No eligible studies were found. There were a few case reports and case series describing successful outcomes with different interventions in this condition. **Authors' Conclusions:** To date, no randomised controlled trial is available that examines the effects of saline irrigation with or without prior hyaluronidase infiltration in the management of extravasation injury in neonates. Saline irrigation is a frequently reported intervention in the literature that is used in the management of extravasation injury in neonates. Research should be initially directed at evaluating the efficacy and safety of this intervention through randomised controlled trials. It will also be important to determine the size of the effect according to timing of intervention, nature of the infusate and the severity of injury at the time of intervention.

DRAFT

References

DRAFT