ORIGINAL ARTICLE

Outsized Treatment Effects of High Potency Polymerized Cross-Linked Sucralfate (ProThelial) for Oral and Gastrointestinal Chemoradiation Mucositis – The Level of Evidence and Implication for National Cancer Center Network Category 2A Recommendations

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ABSTRACT

Background: Chemoradiation mucositis (CRM) of the oropharynx and gastrointestinal tract (GI) leads to intolerance of anticancer treatment, poor quality of life, increased morbidity, mortality, and costs. High potency polymerized cross-linked sucralfate (HPPCLS) has been associated with complete prevention, rapid 2–3 day sustained elimination of CRM and gastrostomy tube aversion but is yet to be evaluated by current mucositis guidelines (CMG) due to incomplete method of evaluation. **Objectives of Report**: (1) Contrast method of assessing evidence used in CMG to that used in a system developed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group. (2) Explain the significance of treatment effect size, of HPPCLS clinical outcomes. (3) Suggest a process to identify studies of patient-centered effectiveness that may be useful to evaluate HPPCLS by NCCN institutions. **Methods to achieve Objectives:** (1) Provide guidance on mucositis guidelines. (2) Review acceptable standards of ranking evidence. (3) Review concepts of effect size and the implications of large treatment effect size of HPPCLS. (4) Provide steps toward NCCN guideline evaluation of HPPCLS. **Results:** Using the Somerfield–Hadorn approach to guideline development, CMG's identifies interventions that do not work. However, the system has an analytical blind spot qualified therapies, lack external validity in highlighting interventions with fractional, clinically insignificant impact in toxicity reduction. GRADE system for ranking evidence embraces the magnitude of treatment effect, corroborating the significance of HPPCLS outcomes which have >5-fold reduction in disease risk, a dose–response gradient, patient-centered outcomes, and interpractice consistency. Given the morbidity and mortality associated with CRM, these initial patient reported outcomes on HPPCLS necessitate formal NCCN clinical evaluation of HPPCLS as a potential Category 2A intervention. **Conclusions:** CMG should be standardized by the GRADE approach of ranking evidence which includes patient-centered outcome measures that improve external validity and rating treatment effect size to eliminate analytical blind spots. Practice-based NCCN institutional evaluations of HPPCLS can be performed with minimal disruption to on-going patient care. Such evaluations can generate a preponderance of data coupled to mucositis biomarkers that might efficiently analyze the implication that HPPCLS be a recommended option for mucositis management.

Key words: Cost of cancer care, gastrointestinal mucositis, medication-use evaluation, oral mucositis, polymerized sucralfate

INTRODUCTION

With a 96–97% reduction in the duration of oral mucositis, rapid 2– 3-day complete elimination of esophageal, intestinal, and colonic mucositis and complete prevention of mucositis onset averting gastrostomy tube placement,[1-7] high potency polymerized cross-linked sucralfate (HPPCLS) has an outsized treatment effect. These effects have implications for cancer treatment guidelines of the National Cancer Center Network (NCCN). The treatment

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effect of HPPCLS also has a dose–response gradient, wherein toxic mucositis recurs when stopped and reverses when HPPCLS is reinstituted.[1] The data source is an observation-designed mucositis registry study, traditionally considered less desirable to randomized controlled trial (RCT) design. However, the quality of HPPCLS evidence is ranked high due to a quantifiable large magnitude of treatment effect associated with a 30-fold reduction in the duration of mucositis in head-and-neck cancer (HNC) patients undergoing chemoradiation.[8]

Evidence standards established by working groups in the Agency for Healthcare Research and Quality (AHRQ) and in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) initiative[9-12] assign grade of evidence based on both study design and on the strength of outcome association, that is, the magnitude of treatment effects. Evidence standards established by working groups in the Agency for Healthcare Research and Quality (AHRQ) and in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) initiative [9-12] has assign grades of evidence based on both study design and on the strength of outcome association, that is, on the magnitude of treatment effects. The AHRQ and GRADE systems will rate evidence up one level for an intervention associated with a two fold reduction in risk. AHRQ and GRADE will rate evidence up two levels for interventions associated with a 5-fold or greater reduction in risk and even higher when an intervention demonstrate a dose-response gradient, especially if anticipated confounders or biases would ordinarily decrease the overall size of the treatment effect.[13]

Interventions with outsized treatment effects are rare, occurring 0.06% of the time.[14] Mucositis guidelines that do not embrace the GRADE criteria have an approach of ranking evidence that fails to account for treatment effect size of an intervention. The deficiency to formally recognize the relevance of effect size in ranking quality of evidence creates an "analytical blind spot" within such guidelines leading to systematic omission of interventions with statistically relevant outsized treatment effects that meaningfully reduced disease risk. Objectifying the manner of rating evidence was, in part, a founding principle of the GRADE criteria.[15] While RCT will always remain the gold standard of evidence, interventions that reliably reduced disease risk by 2–5 fold or greater, demonstrating a dose–response gradient, should qualify for guideline consideration regardless of the study design. This is an accepted evidence-based approach essential to inform the development of guideline recommendations.

In addition, therapeutic options with treatment effects statistically better than placebo, yet are only comparable to placebo and confounders[16] in terms of order of magnitude, do not significantly reduce disease risk and therefore, are of limited or questionable clinical real-world value. Thus, in addition to analytical blind spots, guidelines inconsistent with the GRADE approach fail to provide contextual relevance for recommendations. Contextual relevance of recommendations is key to acceptance in clinical practice.[17,18] Without contextual relevance, a guideline recommendation implies to the reader that the clinical context of an RCT can reliably be transferred into real-world clinical practice. Written disclaimers warning against such assumptions is laudable for transparency but hardly informs a guideline reader in the use of published recommendation. Without contextual relevance, prospective adherents to any proposed recommendation must assume that the quality of evidence transfers unchanged to the heterogeneous real-world settings of clinical practice, an assumption which is often untrue. While this conundrum is not the intent of non-GRADE guidelines, without contextual relevance for recommendations, assumption of generalizability is an unintended consequence and one that is exacerbated when guideline developers actively promoted guideline recommendations to cancer institutions.[19-22] Such guidelines are not included in the NCCN recommendations, in part due to the lack of expert consensus of their clinical relevance. Systematic reviews without relevant contextual definition of the recommendation make resultant guidelines clinically moot as prospective users are paralyzed with questions of the real-world significance of published recommendations. Discontinuing ineffective practices is an evidence-based benefit of non-GRADE mucositis guidelines; however, affirmative deployment of new therapeutic options is less so.

Category 2A recommendations of NCCN differ in structure from most mucositis guideline recommendations. The former uses a lower level of clinical trial data than the latter. Level 1 or Level 2 evidence is used by most mucositis guidelines, while Level 2 or 3 clinical trial data may be used in Category 2A NCCN recommendations. While most mucositis guideline recommendations (Level/Level 2) would be equivalent to the NCCN Category 1, only 8% of most NCCN guidelines are Category 1, with breast cancer guidelines topping at 30%.[23] Well over 80% of NCCN guidelines are Category 2A, comprising of lower level study evidence combined with expert consensus following clinical evaluation of an intervention in a majority of NCCN institutions.[23] Real-world examination of an intervention in the academic settings of NCCN institutions anchors its guideline recommendations. Seemingly, this is a pendulum swing in a direction away from traditional mucositis guidelines which explicitly excludes clinical "expert opinion" as a component of evidence. The risk of corruptibility of expert opinion is real, but controllable, and it represents a valid effort toward providing real-world contextual relevance to guideline recommendations.

Clinical data on HPPCLS is derived from real-world clinical settings where the cancer type, the treatment causing mucositis, the grade and anatomic location of mucositis (oral

versus gastrointestinal [GI]), and the participating clinician (medical vs. radiation oncologist) were uncontrolled. Thus, according to its study design, the HPPCLS data, understandably and appropriately, should be viewed as lower level evidence. However, based on GRADE criteria in rating evidence[13,24] the magnitude HPPCLS's treatment effect in lowering absolute relative risk of 84-day duration of mucositis by 97% and its association with complete prevention of oral mucositis, elevates HPPCLS outcomes to a higher grade of evidence. To date, other than HPPCLS, no therapeutic agent has been associated with complete prevention of all grades of mucositis anticipated in elderly HNC patients undergoing radiation.[7] Except for the lack of expert evaluation by NCCN institutions, HPPCLS would qualify as an NCCN category 2A option for the management of chemoradiation mucositis (CRM) of any grade occurring in any anatomic location.

This report has several objectives. One objective is to describe the approach to evidence commonly used in current mucositis guidelines (CMG), discuss how it differs from the GRADE and AHRQ approaches and then suggest ways to provide contextual relevance to the current guidelines. Another objective of this report is to explain how treatment effect size impacts the level of evidence and use relevant aspects of the HPPCLS registry data to do so. Finally, this report will outline a process for patient-centered effectiveness studies that may be useful for NCCN evaluation of HPPCLS in managing CRM.

METHODS

Methods used in this report are anchored in its objectives. First, in providing guidance on guidelines, contrasted methods in rating evidence will be presented as well as ways to improve external validity of CMG. This will be followed by a graphic illustration of outsized treatment effect, in relation to standard treatment, placebo, and confounding effects. This is a foundational component of the GRADE approach and is sometimes referred to as the Glasziou treatment effect[25] which will be discussed. The graphic will provide a backdrop for a brief review of clinical settings in which HPPCLS has been studied to date. This review illustrates the unexpected failure of uncontrolled factors to adversely affect the uniformity of HPPCLS outcomes – complete prevention, rapid and sustained elimination of toxic mucositis regardless of mucositis severity or anatomic location. Any NCCN Category 2A recommendation will require a process outline for time-efficient institution-based protocols that are patient-centered. This final objective will shape efforts in determining to the value, if any, that HPPCLS may hold for mucositis management.

Guidance on guidelines

Key mucositis guidelines[26-30] are listed in Table 1. The most prominent and enduring of each of these are mucositis guidelines published by the Multinational Association for Supportive Cancer Care (MASCC) Working group. Their method of guideline development depends on the Somerfield–Hadorn approach[31] which develops recommendations based on data gleaned solely from RCT's. MASCC guidelines process begins with a quarrying vast numbers of publications and systematically ranking each in accordance to a method of Somerfield *et al*. as shown in Table 2.[32] Targeted studies are further categorized according to potential for bias, which involves assignments of strengths to data elements using the eight-point Hadorn criteria.[33] Application of the Hadorn criteria which is pre-weighted to prioritize data elements is

Table 1: Guideline working groups for chemoradiation toxic mucositis

Guideline working group	Most recent	Criterion used	Designated support classification	Assign grade of evidence by strength of treatment effect
NCCN	2008	RCT, expert consensus	Strategies for prevention, treatment, and general management	NO
ASCO	2007	RCT, high powered	Recommended	NO
ESMO	2009	RCT, high powered	Recommended; Suggested	NO
ONS	2008	RCT, high powered	Recommended; Likely to be effective; Benefits balanced with harms; Effectiveness not established; Effectiveness unlikely; Not recommended for practice	NO
Cochrane Reviews	2007, 2008	RCT, high, medium powered	Evidence with bias that is low, moderate, and high bias	NO
MASCC	2014	RCT, high powered	Recommended; Suggested; No Guideline Possible	NO

NCCN: National Cancer Center Network, ASCO: American Society of Clinical Oncology, ESMO: European Society of Medical Oncology, ONS: Oncology Nursing Society, MASCC: Multinational Association for Supportive Cancer Care, RCT: Randomized controlled trial

a highly structured, time-consuming, and arduous process executed in a disciplined manner by MASCC for years. The culmination of the Somerfield–Hadorn approach is a systematic review of peer-reviewed literature identifying interventions that work and those that are likely not to work. Clearly, recommendations against the use of ineffective interventions are the first fruits of this effort. The MASCC Working group has successfully identified many agents used before 2004 as ineffective. Nearly, all agents used before 1995[34] such as magic mouthwash, antimicrobials, coating agents, and off-labeled use of pharmaceuticals were identified by MASCC as ineffective and therefore wasteful of resources.[35] These are easily adopted at an institutional level.

However, positive recommendations for interventions are a challenge to implement institutionally. First, outcomes upon which recommendations are based, are statistically significant, but lack meticulous consideration on the strength of association which limits the clinical relevance of guideline recommendations. In fact, most of the MASCC recommendations are for 12 interventions provide only fractional benefit in highly controlled settings.[30] The probability that identical controlled setting reoccur in clinical practice is low.

Table 2: Somerfield *et al.* levels of evidence used by most mucositis guidelines

I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power)
II	Evidence obtained from at least one well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies, such as non-randomized, controlled single-group, pretest-posttest comparison, cohort, time, or matched case–control series
IV	Evidence obtained from well-designed, non-experimental studies, such as comparative and correlational descriptive and case studies
V	Evidence obtained from case reports and clinical examples

Recognizing the limitation of existing guidelines in 2004, early proponents of the GRADE Working Group conducted a critical appraisal of guideline approaches similar to Somerfield–Hadorn.[15] Having established consensus on the inadequacy of current approaches, GRADE working group crafted a system for rating quality of evidence as rigorous as the Somerfield–Hadorn method, that was astute and contextually relevant to patient-centered outcomes.[36] The GRADE approach reaffirmed RCTs as the gold standard for high-level evidence and observational studies as lower level of evidence. However, by focusing efforts on defining and characterizing an intervention's strength of association to an outcome, GRADE broadened the review of interventions. Regardless of the quality of study design, the final arbiter of evidence level is the strength of association of an intervention with the outcome of interest.

In contrast to this position, the litmus test and single source of high-level medical evidence in the Somerfield–Hadorn approach is the RCT. Clearly, academic practitioners of evidence-based medicine do not agree. Focusing on an intervention's strength of association, the GRADE Working Group[12,15,25,36] and its adherents[37] upgrade the evidence level for interventions in observational studies if the outsized treatment effects reduce disease risk by 2–5 fold or greater, there is a dose–gradient effect, and anticipated confounders would lower the magnitude of treatment effect.[13] Between 85% and 95% of HNC patients undergoing radiotherapy develop oral mucositis lasting on average of 70–84

Table 3: Domains used in deciding on quality of evidence

Factors	Mucositis guideline domains	Complete evidence-based domains
	MASCC/Hadorn method	**GRADE working group**
1	Selection of patients	Study limitations
2	Allocation of patients to treatment groups	Inconsistency of results
3	Therapeutic regimens	Indirectness of evidence
4	Study administration	Imprecision
5	Withdrawals from study	Publication bias
6	Patient blinding	Factors the increase quality
7	Outcome measurement	Large magnitude of treatment effect
8	Statistical analysis	Plausible confounding, which would reduce treatment effect
9		Dose–response gradient

MASCC: Multinational Association Supportive Cancer Care.[23] Hadorn *et al.*[22] GRADE: Grading of Recommendations Assessment, Development and Evaluation

days.[38,39] The 30-fold reduction in the duration of mucositis with HPPCLS observed in HNC patients undergoing chemoradiation[8] and its dose–effect justifies substantial upgrade of the level evidence under the GRADE system. Under Somerfield–Hadorn criteria, HPPCLS is invisible and not qualified for guideline consideration; however, this disqualification misses the fact that the risk of harm from the disease process is reduced 30-fold.

Somerfield–Hadorn versus GRADE criteria of rating evidence

Contradistinctive to Somerfield–Hadorn, the GRADE system[12] is an inclusive system using nine factors to characterize the quality of evidence. Table 3 provides a comparison of the factors used by the two systems. Somerfield–Hadorn uses 8 items of evidence characterization, five of which are subsumed within a single item within GRADE. Since five Somerfield–Hadorn criterions (factors 2, 4, 5, 6 and 7) are included within one GRADE criterion, the comparison is more lopsided with Somerfield–Hadorn approach effectively espousing four criterions compared to GRADE's nine. Furthermore, by design, four of the nine factors identified by GRADE permits evaluation of data from observational studies, wherein outcomes can be rated as high-quality evidence based on the several features related to the intervention's strength of association. The key

Table 4: Criteria for assigning grade of evidence according to guideline working group

Type of evidence (study) & method of rating strength of association	Guideline working groups		
	MWGG	AHRQ	GRADE
Type of evidence			
Randomized trial – high	√	√	√
Observational study – low	√	√	√
Any other evidence – very low	√	√	√
Decrease grade if	√	√	√
Serious (–1) or very serious (–2) limitation of the study	√	√	√
Important inconsistency (–1)	√	√	√
Some (–1) or major (–2) uncertainty about directness	√	√	√
Imprecise or sparse data (–1)	√	√	√
High probability of reporting bias (–1)	√	√	√
Increase grade if	No	√	√
Strong evidence of association (outsized effect [+1])	No	√	√
Significant relative risk >2 based on 2 or more observational studies	No	√	√
Very strong evidence of association (outsized effect [+2])	No	√	√
Significant relative risk >5 based direct evidence with no major threats to validity (single observational study)	No	√	√
Very strong evidence of association (outsized effect [+2])	No	√	√
Significant rate ratio ≥ 10 (single observational study)	No	√	√
Evidence of dose response gradient (+1)	No	√	√
All plausible confounders would have reduced effect (+1)	No	√	√

Adapted from Atkins *et al*.[20] GRADE: Grading of Recommendations Assessment, Development and Evaluation, AHRQ: Agency for Healthcare Research and Quality, MWGG: Multinational Association Supportive Cancer Care Working Group Guidelines

Table 5: Converting internal validity to external validity as basis for guideline recommendations

Stratified expectation of prevention			Stratified expectation of reversal		
Extent of prevention	Low (%)	High (%)	Extent of reversal	Low (%)	High (%)
Minimal	4	15	Minimal	4	15
Partial	16	35	Partial	16	35
Moderate	36	55	Moderate	36	55
Moderately complete	56	85	Moderately complete	56	85
Complete	86	100	Complete	86	100

factor in an intervention's strength of association is that is the quantitative magnitude of the treatment effect. Thus, the exclusion of treatment effect size creates an analytical blind spot for the Somerfield–Hadorn, which in turn limits the value of its systematic review.

Table 4 details the differences between the two systems in assigning grade of evidence. As in the use of risk ratios, in the Cochrane system,[40] there should be some accountability for an intervention's effect size or strength of the association.

Achieving external validity: From systematic reviews to recommendations

Systematic reviews create cohorts of vetted data with statistically strong internal validity. Clinical guidelines that recommend against using an intervention that does not work in RCT would likely have external validity in the real world setting of uncontrolled factors. However, developing recommendations for proactive use of intervention require non-statistical assumptions on the expected or required outcome for the guideline user. The GRADE Working Group urge developers[12,36] to make judgments regarding the appropriateness of evidence quality relative to specific patient-centered outcomes required by guideline users. This step involves external validity. External validity of a guideline recommending the use of an intervention is conferred when vetted data has been subjected to the expectations of patient-centered outcomes and stratified according to the anticipated effect on the disease state. Tables 5 and 6 provide examples of patient-centered outcomes stratified by grade of clinical expectation of those with CRM. Moreover, by stratifying an intervention's effect size by degree of prevention, degree of reversal and time required to achieve reversal, then a vetted cohort of trial data can be converted into guidelines relevant to the clinical expectations of guideline users. Without a method similar to that shown in Tables 5 and 6, a method that stratifies real-world clinical expectation of prevention or reversal, then the external validity for any Somerfield–Hadorn mucositis guideline will be questionable. External validity of guideline recommendation for any intervention is carried by some sense of degree of anticipated clinical outcome. Most Somerfield-Hadorn guidelines fail to serve clinicians' anticipation of expected clinical outcome. Using the recommendations of the guideline, the clinician should have some sense of the degree of anticipated outcome. Lacking this quality injures the external validity of many Somerfield-Hadorn guidelines.

Treatment effect size – the AHRQ, GRADE, and Glasziou effect size

Treatment effect size involves the statistically significant difference between an intervention and its comparator as well as the quantitative magnitude of the treatment effect the intervention has on the disease process. Both statistical difference and the overall magnitude of the effect assess the strength of association. The effect size of most interventions are small and generally within the same order of magnitude as placebo[16] but better than that of confounders/biases.[41] Consequently, 99.96% of interventions demonstrate only a fractionally reduction of absolute disease risk.[14] The gross magnitude of treatment effect for most interventions, while statistically significant, is generally small, is within the same order of magnitude as placebo, though much better than that of confounders/biases, yet with mere fractional impact on disease risk. The 12 interventions supported by MASCC mucositis guidelines [Table 7] is of this class.

Although it has accepted MASCC mucositis guideline interventions [Table 7] into the National Guideline Clearinghouse, the AHRQ endorses and has adopted[9-11] the GRADE criteria for ranking level of evidence which acknowledges the magnitude of treatment effect as a measure of strength of association and ultimate level of evidence. Mentioned earlier and shown in Table 4, this approach to rating strength of evidence involves designating outsized treatment effects from observational studies as evidence of high quality, depending on the magnitude of the effect. It should be borne in mind that the magnitude of treatment effect reflects the reduction of disease risk. For GRADE if treatment effect is associated with a 2–5 folder or greater reduction in disease risk, is dose-dependent, reproducible, and consistent, then the level of evidence is rated up.

The Glasziou theory of rate ratio of outsized treatment outcomes in observational studies[25] is another measure of treatment effect, more stringent than the GRADE method of rating up evidence. It too has been adopted by the AHRQ, NCCN, and the American College of Chest Physicians. Glasziou *et al*.[25] reported that treatment effect sizes are high-grade evidence of showing causality with p value of at least ≤0.05 if their effect size is equal to or >1000 base points beyond placebo (or any other comparator) or beyond the expected time course of the disease. Glasziou asserted that it is statistically improbable that placebo or any confounding bias (blinding, concealment, selection, etc.) could explain the treatment effect in the order of magnitude that is 1000 base points or higher. The impact to reduction of disease risk is far greater in the Glasziou treatment effect than that discussed in the GRADE system.

Table 6: External validity for speed of reversal

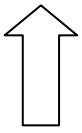
Acceptance	Patient-centered value	Days to reversal
	Highest	1–2 days
	Moderately high	3–4 days
	Moderate	5–7 days
	Moderately low	8–10 days
	Lowest	11–20 days

Table 7: MASCC guideline recommendation/suggestions for 2014

Intervention	Dose/timing	Route	Indication	Intent	Cancer treatment	Other controlling conditions
Gastrointestinal mucositis						
Amifostine	Unmentioned	IV	GIM-esophagitis	Prevention	NSC lung cancer	Concomitant chemoradiation
Sulfasalazine	500 mg bid	Oral	GIM-enteropathy	Prevention	Unmentioned	Pelvic radiation
Octreotide	>100 g	SQ	GIM-diarrhea	Treatment	HSCT	Std/high-dose chemotherapy
Probiotics	UM	Oral	GIM-diarrhea	Prevention	Pelvic malignancy	Chemoradiation therapy
Amifostine	>340 mg/m^2	IV	GIM-radiation proctitis	Prevention	Unmentioned	Receiving radiation therapy
Sucralfate	Unmentioned	Enema	GIM-chronic radiation proctitis	Treatment	Unmentioned	Patients with rectal bleeding
Hyperbaric O_2	Unmentioned		Radiation-induced proctitis	Treatment	Solid tumor	Radiation for solid tumor
Oral mucositis (stomatitis)						
Cryotherapy	30-min prior	Oral	Oral mucositis	Prevention	Unmentioned	Receiving bolus 5-FU
Cryotherapy	Unmentioned	Oral	Oral mucositis	Prevention	HSCT	High-dose melphalan +/- total body radiation
LLLT	650.0 nm	Oral	Oral mucositis	Prevention	HSCT	High-dose chemo +/- total body radiation
LLLT	632.8 nm	Oral	Oral mucositis	Prevention	HNC	Radiation +/- chemo
Palifermin	Protocol	IV	Oral mucositis	Prevention	HSCT	High-dose chemo plus Total body radiation
Benzydamine	0.5%	Oral Rinse	Oral mucositis	Prevention	HNC	Mod radiation<50 gy Without chemotherapy
Zinc	Unmentioned	Oral	Oral mucositis	Prevention	Oral cancer	Radiation or chemotherapy
Oral hygiene	Unmentioned	Oral	Oral mucositis	Prevention	All cancers	All treatment modalities in all age groups
Pain attenuation						
Morphine	Unmentioned	IV	Mucositis pain	Treatment	HSCT	High-dose chemo+/-total body radiation
Fentanyl	Unmentioned	Transdermal	Mucositis pain	Treatment	Unmentioned	High-dose chemo+/-total body radiation
Morphine	2% solution	Oral rinse	Mucositis pain	Treatment	HNC	Chemoradiation
Doxepin	0.5% solution	Oral rinse	Mucositis pain	Treatment	Unmentioned	Unmentioned

HNC: Head-and-neck cancer, HSCT: Human stem cell transplant, IV: Intravenous; LLLT: Low-level laser therapy, NSC: Non-small cell, SQ: Subcutaneous, MASCC: Multinational Association of Supportive Care in Cancer. Used by permission from Euro J Oncol Pharma 2015.[26]

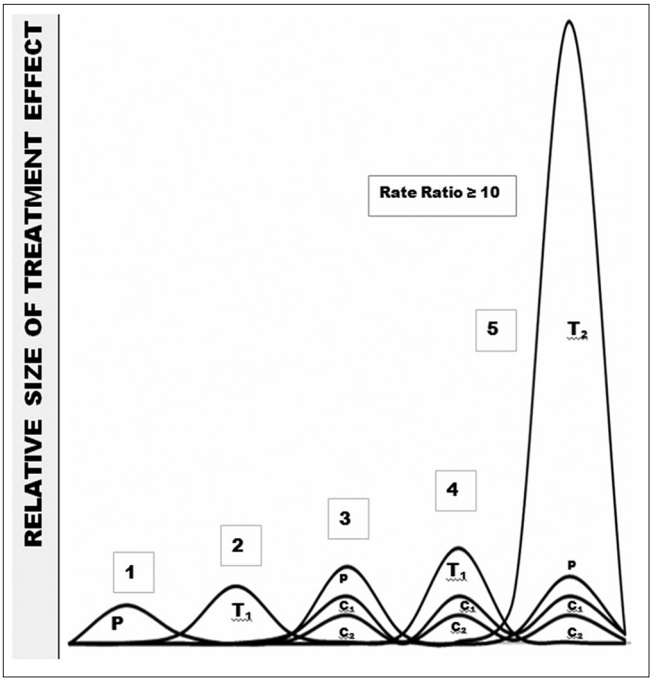


Figure 1: Peak T_2 illustrates a positive Glasziou treatment effect. Peak 1, P is the size of the placebo effect controlled by blinding and randomization (randomized controlled trial [RCT]). Peak 2, T_1 is the treatment effect size of intervention #1 controlled by blinding and randomization (RCT). Peak 3, P+C1+C2 is the size of the placebo effect with poor/no blinding (C1) and poor/no randomization (C2). Peak 4, T1+C1+C2 is the treatment effect size of Intervention #1 with poor/no Blinding (C1) and poor/no Randomization (C2). Peak 5, T2+C1+C2 is the treatment effect size of Intervention #2 with poor/no Blinding (C1) and poor/no Randomization (C2). C1+C2 are confounding bias such as blinding and randomization. Used by permission from Mueller Medical International © 2017

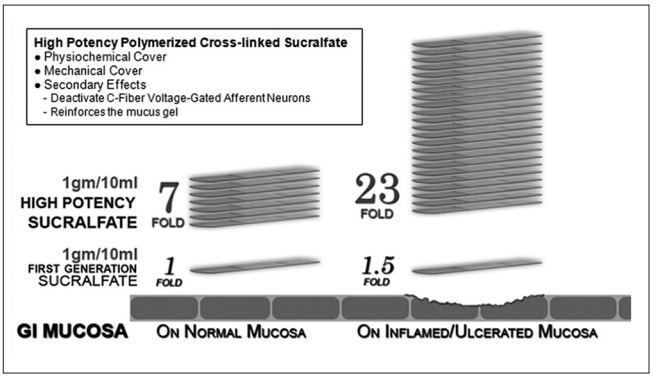


Figure 2: Prolonged exaggerated surface concentration of high potency polymerized cross-linked sucralfate 3 h post dosing. Used by permission from Mueller Medical International © 2012

Graphic illustration of positive Glasziou treatment effect

The Glasziou treatment effect is schematically illustrated in Figure 1 where it is compared to the treatment effects of standard interventions in RCT. Respectively, Peaks 1 and 2, the represent the effect size of placebo (labeled "P" in Peak 1) and the effect size of treatment 1 (labeled T_1 in Peak 2). In both peaks (Peak 1 and 2) there is maximal control of all bias or confounding factors. Peaks 3 and 4 illustrate how uncontrolled confounding factors labeled C_1 and C_2 augment the effect size of placebo and treatment 1 (T_1). Both C_1 and C_2 represent the lack of randomization, concealment, or blinding in the study design. Peak 5 represents the minimal size of a positive Glasziou treatment effect from intervention in an observational study. Obviously the effects of placebo (P) or confounders (C1 and C2) contribute very little to the magnitude of the overall effect of treatment no. 2 (labeled T_2). Obviously minimizing or eliminating all confounding factors in Peak 5 would not appreciably affect the magnitude of the intervention's treatment effect. This is why Glasziou *et al*.[25] asserted that the RCT outcomes on these interventions would be predictably unchanged from the observational outcomes due solely to their magnitude of effect, that is, their strength of association.

The 12 MASCC supported interventions listed in Table 7 are from RCT's having treatment effect sizes that are, at best, similar to Peak 2 (MASCC Level 1 evidence) and at worse, similar to Peak 4 (MASCC Level II/III). The strength of association is anchored by a statistical difference from placebo that is consistently and reproducibly observed in an adequate number of patients per treatment arm. Such interventions are either MASCC recommended or suggested for clinical use even though the reduction in disease risk is only fractional. Since treatment 2 (T_2) in Peak 5 was derived from an observational study the Somerfield–Hadorn approach employed in MASCC guidelines would exclude treatment no. 2 from consideration, though clearly the magnitude of its treatment effect demonstrates a substantial reduction in disease risk.

Interventions with positive Glasziou treatment effects

Interventions with outsized treatment effects are rare occurring 0.06% of the time.[14] Positive Glasziou treatment effects are even more uncommon but do exist. The use of injectable insulin for hyperglycemia to repeatedly, predictably, and consistently lower blood sugar is an intervention with a positive Glasziou treatment effect and does not widely vary with prescriber or patient. The use of edrophonium to repeatedly, predictably, and consistently, reverse myasthenia gravis (the Tensilon test) is an intervention with a positive Glasziou treatment effect. The effect size of insulin and edrophonium is far >1000 base points beyond placebo or the natural course of either disease and is associated with a substantial reduction in disease risk. It is not an evidence-base principle to insist on RCT's in order to believe the strength of outcome association with an intervention, when the magnitude of the outcome reduces the risk of disease by 5 fold or greater. For patients receiving chemoradiation

the Glasziou rate ratio for HPPCLS in reducing mucositis duration by 97% is over 6000 base points beyond placebo, other comparators or the natural resolution of mucositis. It is statistically improbable that factors other than HPPCLS treatment effect could be responsible for the observed outcome. The strength of association is further aided by the dose–response gradient of HPPCLS and its reproducibility in diverse and heterogeneous clinical settings, which in general are uncontrolled factors that blunt treatment outcomes.[42]

HPPCLS outcomes

HPPCLS

HPPCLS is a potency-enhanced formulation of sucralfate that has been polymerized and cross-linked to achieve an exaggerated high surface concentration of sucralfate. It is the only FDA licensed alternative non-pill form of standard sucralfate. Three hours post-administration, HPPCLS maintains surface concentrations of sucralfate that are 800% higher on normal mucosa and 2400% higher on injured mucosal lining[43] as illustsrated in Figure 2. Since sucralfate is a non-systemic, topically active agent with a device mechanism of action, enhanced surface concentration from HPPCLS over standard sucralfate, not only implies increased potency but also anticipated enhanced clinical effects. Complete prevention of the onset of radiation-induced mucositis by an intervention is unanticipated in elderly HNC patients undergoing daily radiation. Likewise, rapid sustained elimination of mucositis by an intervention is unanticipated once mucositis has been established in patients undergoing daily radiation. Ability to reverse Grade 1–3 mucositis within 2–3 days in oral and GI locations is also unexpected.

HPPCLS outcomes reproducible in diverse and heterogeneous clinical settings

The diversity of oncologists, geographic regions, types of cancer, treatment regimens, severity and anatomic location of mucositis are uncontrolled factors in the real-world clinical practice. Conventionally, observational designs have biases related to recall, interviewer, follow-up, and misclassification, which can increase the treatment effect. Biases related to sampling, study execution, and data collection can affect treatment outcome either way. Variability in patient age, gender, geographical residence, regional, and clinical setting of oncology practice are potential confounders that may tend to exert downward pressure on treatment outcomes.[42,44,45] The non-uniformity and diversity of uncontrolled factors

Table 8: HPPCLS protocol using for chemoradiation-induced mucositis

Management goal	Cancer therapy	Loading dosing	Maintenance dosing through 1-week post-cancer therapy
Treatment Grade 1, 2	Chemoradiation	2.5–5ml TID×1 day (250–500 mg)	2.5–5 ml BID (250–500 mg)
Treatment Grade 3, 4	Chemoradiation	10 ml TID×2 days (1000 mg)	5–10 ml BID (500–1000 mg)
Prevention Grade 1, 2	Chemoradiation	2.5–5 ml TID×1 day (250–500 mg)	2.5–5 ml BID (250–500 mg)
Prevention Grade 3, 4	Chemoradiation	10 ml TID×2 days (1000 mg)	10 ml TID (1000 mg)

Prevention regimen start the first day of cancer treatment; BID is twice daily; TID is three times daily. HPPCLS: High potency polymerized cross-linked sucralfate

Table 9: ProThelial efficacy in a glance – toxic mucositis registry study

Number of oncologists	39 (26 radiation oncologists/13 medical oncologists)
Number of medical centers	32
Number of states in the US	14
Number patients	66
Types of cancers	Melanoma, lymphoma, sarcoma, lung, colon, pancreas esophagus, larynx, tonsil, tongue, squamous cell head neck
Type of anti-cancer agents	15 (with 5 immunotherapies)
Type of toxic mucositis	53 with oral, 41 with GI mucositis
Number Grade 1, 2 mucositis	29 with oral mucositis
Number Grade 3, 4 mucositis	17 with oral, 41 with GI mucositis
Prevention efficacy	8 out of 8 or 100%
2–3 day rapid and sustained elimination	53 out of 58 or 91%
Percent reduction in days of toxic mucositis	96–97%
Statistical significance for the effect size	P=0.001, at 95% confidence, two-sided

GI: Gastrointestinal

Table 10: Types of cancers with mucotoxicity using HPPCLS in registry to eliminate/prevent mucositis

Cancer Type	Number of Patients	Therapy	Antimucositis Agent	Outcome*
For mucositis reversal				
SCCHN (undifferentiated)	18	Radiation (and chemotherapy)	HPPCLS	2–3-day elimination
SCCHN (tongue)	10	Radiation (and chemotherapy)	HPPCLS	2–3-day elimination
SCCHN (tonsil)	8	Radiation (and chemotherapy)	HPPCLS	2–3-day elimination
SCCHN (oral cavity)	4	Radiation (and chemotherapy)	HPPCLS	2–3-day elimination
SCCHN (larynx)	5	Radiation (and chemotherapy)	HPPCLS	2–3-day elimination
Esophageal	2	Radiation (and surgery)	HPPCLS	2–3-day elimination
Pancreatic cancer	2	Chemotherapy	HPPCLS	2–3-day elimination
Colon cancer	2	Chemo (and surgery)	HPPCLS	2–3-day elimination
Lung cancer	2	Chemotherapy (and radiation)	HPPCLS	2–3-day elimination
Bladder cancer	1	Chemotherapy	HPPCLS	2–3-day elimination
Ovarian cancr	1	Chemotherapy	HPPCLS	2–3-day elimination
Soft-tissue sarcoma	1	Chemotherapy (and radiation)	HPPCLS	2–3-day elimination
Lymphoma	1	Chemotherapy (and radiation)	HPPCLS	2–3-day elimination
Metastatic melanoma	1	Chemotherapy (and surgery)	HPPCLS	2–3-day elimination
For mucositis prevention				
Tongue (SCCHN)	2	Radiation (and chemo)	HPPCLS	Complete prevention
Oral cavity (SCCHN)	3	Radiation (and chemo)	HPPCLS	Complete prevention
Larynx (SCCHN)	1	Radiation (and chemo)	HPPCLS	Complete prevention
Tonsil (SCCHN)	2	Radiation (and chemo)	HPPCLS	Complete prevention

*Some patients still experienced dry mouth (salivary gland dysfunction), altered taste, and dental issues. None of these are related to disruption of the mucosal lining of the oral, pharyngeal, and esophageal cavity. HPPCLS: High potency polymerized cross-linked sucralfate

were not reflected in HPPCLS outcomes, where all patients experienced 2–3-day reversal of CRM sustained throughout chemoradiation course.

Mucositis registry in real-world clinical settings

As part of post-approval obligations to the FDA, a Mucositis Registry was populated from February 10, 2014 to December 30, 2014. It included 66 sequentially enrolled cancer treatment patients who either had or were anticipated to develop CRM by their oncologists. Prescribers were self-selected based on their interest in managing treatment-related mucositis. Primary outcomes of interests were safety/adverse drug events, patients' tolerance of HPPCLS, physician use pattern, and management intent (mucositis prevention and mucositis reversal).

The HPPCLS dosing protocol used by oncologists in Table 8 reflects the dose required to prevent or reverse mucositis of any anticipated severity.

Diverse practice setting

There were 39 oncologists (26 radiation oncologists and 13 medical oncologists) from 32 participating institutions across 14 states in the US including Connecticut, Florida, Georgia, Illinois, Kansas, Massachusetts, Maine, Michigan, New York, Pennsylvania, Rhode Island, Tennessee, Texas, and Washington. The type of oncology practices included National Cancer Institute designated facilities (n = 4), NCCN practices (n=2), hospital-based institutions (n = 20), and community-based practices (n = 6). Table 9 provides a summary of the HPPCLS registry study with outcomes, which have been reported elsewhere.[1-7]

Diverse clinical causes of mucositis

CRM in the oropharynx, esophagus, and small and large intestine was caused by 15 anticancer therapies: standard radiation and intensity modified radiation, either alone or in combination with ipilimumab, nivolumab, cetuximab, bevacizumab, pazopanib, folinic acid, 5-fluorouracil, irinotecan, oxaliplatin, carboplatin, cisplatin, paclitaxel, and gemcitabine. The types of cancer under treatment, the multiple anticancer regimens used and the severity and anatomical location of resulting mucositis are provided in Tables 10-12, respectively.

Near identical registry outcomes

The outcomes of the HPPCLS Mucositis Registry reported previously[8,46] are shown in Tables 10, 12, and 13. No adverse reactions were encountered and HPPCLS was well

tolerated. Five patients were lost to follow-up. Regarding physician's direction of use, 48 of the 61 patients reporting outcomes (or 78.7%) were instructed by prescribers to swallow HPPCLS (an off-label instruction) rather than expectorate following application and gargling. This was done to manage mucositis of the esophagus, small intestine, and colon. HPPCLS prevented the onset of mucositis [Table 13] in all eight elderly head neck cancer patients (age 74–93). The physicians' prevention intent in mucositis management was to avert placement of gastrostomy feeding tubes. Although the patient cohort is same, the prevention rate of 100% was a reproducible effect occurring among 3 separate oncologists with no collaborative communications in clinical practices located in different geographical regions. The 53 patients with Grade 1 oral mucositis reported reversal in 1–2 days; for Grade 2–3 reversal occurred in 2–3 days. In three studies involving 351 patients, patient-reported complete resolution of oral mucositis took 70–84 days.[38,39,47] In patients using HPPCLS, Grade 2–3 oral mucositis was reversed in 2–3 days representing a 96–97% reduction in mucositis duration and a Glasziou rate ratio score of 67.8, that is 6780 base points better than otherwise would be expected. This outsized treatment signals occurred in patients with mucositis involving the oropharynx, esophagus, and distal GI tract beside those with complete prevention.

Table 11: Agents used in Mucositis Registry causing Toxic Mucositis

Standard radiation	Oxaliplatin	Cetuximab
Intensity-modified radiation	Paclitaxel	Ipilimumab
Cisplatin	5-fluorouracil	Nivolumab
Carboplatin	Folinic acid	Pazopanib
Gemcitabine	Irinotecan	Bevacizumab

Implications for NCCN Category 2A guideline status

The strength of association for HPPCLS outcomes have implications for NCCN management guidelines for patients where chemoradiation challenges tolerance of cancer treatment regimens. Besides the painful, debilitating experience of chemoradiation toxic mucositis (CRTM), there are at least 47,000 mucositis-associated annual deaths[48] mostly due to earlier unplanned treatment breaks. Since unplanned treatment breaks dilute the dose density of chemoradiation, the clonogenic repopulation of tumor cells during breaks lead to a lower 5-year survival.[49-55] Among certain HNC patients, an unplanned break as little as 3 days in a 42-day course can lower 5-year survival from 65% to 18%.[53] Of the 1.6 million newly diagnosed cancer patients in the US, 522,166 undergo chemoradiation, of which 234,542 develop significant grades of mucositis that involve the oropharynx, esophagus, and small bowel.[48] Complete prevention or rapid sustained elimination of CRTM would reverse adverse outcomes for a specific cohort of patients and reduce downstream costs of care. Thus, the NCCN evaluation of HPPCLS for a potential mucositis management role may be appropriate (a) for HNC undergoing chemoradiation, (b) for the use of highly mucositogenic therapies (e.g., those used in pancreatic and colorectal cancer), and (c) for diseases requiring human stem cell transplantation.

Table 12: Baseline types (location) and grades mucositis in radiotherapy patients

Location mucositis	Grade	Patients *n*=53	Grade system	Outcome elimination
Oral mucositis	Grade 1	8	WHO	1 day
	Grade 2	28	WHO	2–3 days
	Grade 3	17	WHO	2–3 days
	Grade 4	0	WHO	
Esophageal mucositis*	Grade 2	20	WHO/EORTC-RTOG	2–3 days
Small bowel mucositis*	Grade 2	10	WHO/EORTC-RTOG	2–3 days
Colonic mucositis*	Grade 2/3	11	WHO/EORTC-RTOG	2–3 days

*Some patients had mucositis in several anatomical areas (oral, esophageal, small bowel, and colon). WHO: World Health Organization, EORTC-RTOG: European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group

Table 13: Radiotherapy patients with SCC using HPPCLS in registry to prevent mucositis (age 74–93)

Cancer type	Number of patients	Therapy	Prevention agent	Mucositis
SCCHN (tongue)	2	Radiation (and chemo)	HPPCLS	G-tube averted
SCCHN (tonsil)	2	Radiation (and chemo)	HPPCLS	G-tube averted
SCCHN (oral)	3	Radiation (and chemo)	HPPCLS	G-tube averted
SCCHN (larynx)	1	Radiation (and surgery)	HPPCLS	G-tube averted

HPPCLS: High potency polymerized cross-linked sucralfate

NCCN institutional review of HPPCLS

The NCCN guidelines address more than 97% of cancers affecting patients in the United States. They incorporate real-time updates in accordance with the rapid advancements in oncology. The guidelines impact decision-making in cancer care impacting physicians, nurses, pharmacists, payers, patients, and their families. Annual reviews of institutional members make NCCN guidelines a living document with expert consensus that stems from the institutional familiarity with any given intervention.

Any approach to an institutional review for HPPCLS would involve (a) considering current institutional regimens for mucositis and their efficacy, (b) a method of introducing HPPCLS with minimal disruption of ongoing patient care, (c) an experimental evaluation (RCT) of HPPCLS in a targeted cohort of patients, and (d) peer-reviewed presentation of institutional outcomes.

Due in large part to the lack of effective therapeutic options that could be prescribed, mucositis management has been the clinical responsibility of the nursing staff and mid-level practitioners, (such as nurse practitioners, physician assistants, or oncology pharmacists).[34] Consultation with oncology dentists and guidance from oncology nurse guidelines[27] have aided in mucositis management. However, following the 2008 NCCN mucositis guideline initiative,[26] there has been little in the way of a standard NCCN-wide endorsed protocol or approach to mucositis management.

Existing institutional protocols versus baseline incidence

Wherever institutional protocols for mucositis management exist, efficacy measures should be available. However, without an existing protocol, then a prospective study of baseline incidence of mucositis will be required. A baseline prospective study will provide a historical experience to serve as an institutional baseline. In other words, *in lieu* of baseline data on the efficacy of existing protocols, an institution-based evaluation of HPPCLS will likely begin with a 3–6 month monitoring period to document the institutional incidence and severity of mucositis in vulnerable patient populations - HNC patients receiving chemoradiation, HSCT patients, and those receiving chemo for pancreatic and colorectal cancer. A validated outcome measure might include the use of the mucositis daily questionnaire (MDQ) employed by Elting *et al*.[47] which simultaneously assesses the daily quality of life, daily GI tract function, and daily mucositis pain.

Minimally disruptive introduction of HPPCLS

The initial introduction of HPPCLS should not disrupt ongoing patient care. Mucositis registry data recording patients' experience of using HPPCLS as part of their course of cancer treatment is not interventional and is minimally disruptive, as the actions are kept and reported within the sphere of a treating clinic. It could represent a reasonable first step. While on HPPCLS, targeted patient cohorts can complete the validated MDQ used by Elting *et al*.[47] This would be particularly useful in comparing against MDQ baseline incidence and severity measures mentioned above.

Experimental evaluation of HPPCLS

Experimental evaluation of HPPCLS can involve two types of interventional studies. The first type would be the continuation of the mucositis registry with MDQ data but correlated biomarker cytokine profile from patients' saliva or serum samples. Biomarker correlation could be added to the baseline studies mentioned already as well as to the steps of minimally disruptive use of HPPCLS. The second type of experimental evaluation could involve RCT of patients using institutional protocol alone and using institutional protocol plus HPPCLS. Again validated MDQ would be used as a primary outcome measure. Biomarker correlation would be an additional dimension to HPPCLS outcomes.

Other validated outcome measures can include oral mucositis assessment scores,[56] World Health Organization,[57] and the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group grading scales[58] for oral and GI mucositis assessments.

In HSCT patients the experience of intestinal bacteremia is thought to result from intestinal mucositis of the colon and small bowel, rather than resulting from neutropenia[59]. Therefore, using validated outcome measures to assess the change in bowel susceptibility,[60] to mucositis while on HPPCSL would be useful, and particularly insightful if clinical effects are correlated with inflammatory biomarkers in saliva, serum, or feces of HSCT patients. Table 14 provides an overview of other elements regarding NCCN institutional evaluation of HPPCLS.

Peer-reviewed presentation of institutional data

Peer-reviewed presentation of institutional data to medical associations is important in the process of vetting HPPCLS data, particularly its clinical usefulness. Oncology-wide critique of HPPCLS can only be beneficial for all pertinent stakeholders – patients and loved ones, practitioners, and payers.

CONCLUSIONS AND SUGGESTIONS

Whether using the Somerfield–Hadorn system or GRADE, a disciplined systematic review of published investigations

Table 14: Investigation of HPPCLS to establish institution-based mucositis protocols

Investigation team members	Team 1 RN/NP/or PA+radiation oncology fellow/resident Team 2 RN/NP/or PA+medical oncology fellow
Study type	(1) Observational using sequential/consecutive randomization (2) Interventional using sequential/consecutive randomization
Comparators	(1) Existing institutional mucositis protocol procedures (2) Known institutional historical outcomes (3) Active comparator – oral care
Outcome measure tools	(1) Mouth–throat soreness questionnaire (2) WHO and EROTGC oral and GI toxicity scales (3) OMAS
Treatment modality patient population	Head-and-neck cancer radiotherapy patients – outcomes of interest
	(1) Oropharyngeal/esophageal mucositis – complete prevention (2) Oropharyngeal/esophageal mucositis – complete elimination
	Human stem cell transplantation patients – outcomes of interest
	(1) Oropharyngeal/esophageal mucositis – complete prevention (2) Oropharyngeal/esophageal mucositis –complete reversal (3) Febrile intestinal mucositis – complete prevention (4) Febrile intestinal mucositis – complete reversal
Toxicity management population	
Radiation GI toxicity management	Rate of reversal studies
	(1) Radiation esophagitis in treating thoracic cancer (2) Radiation enteritis in treating intestinal/colonic cancer (3) Radiation proctitis in treating pelvic cancer
Chemotherapy GI toxicity management	Rate of reversal studies
Chemotherapy induced	(1) Esophagogastritis and intestinal/colonic mucositis – pancreatic cancer
Chemotherapy induced	(2) Nausea and vomiting – mitigation or reversal
Chemotherapy induced	(3) Diarrhea – mitigation or reversal

HPPCLS: High potency polymerized cross-linked sucralfate, GI: Gastrointestinal, WHO: World Health Organization, EORTC: European Organization for Research and Treatment of Cancer

will provide a vetted cohort of data that credibly identify which interventions do not work in RCT. Then, depending on the criteria used to assign grade of evidence vetted data may further identify interventions that work.

It is clear that Somerfield–Hadorn system has an analytical "blind spot" to interventions in observational studies with positive Glasziou treatment effects [Peak 5 of Figure 1]. In addition to an analytical "blind spot," mucositis guidelines influenced by Somerfield–Hadorn provide little or no clinical context beyond that in RCT's evaluated. So while having internal validity, such guidelines lack external validity that limits use in clinical practice.

Stratifying the strength of association (effect size) of any given intervention according to expectation of prevention or reversal [Table 5] and providing patient-centered anticipation on the speed of reversal [Table 6] can help provide external validity to Somerfield–Hadorn guideline recommendations.

The sheer size of HPPCLS treatment effect elevates its level of evidence. HPPCLS appears to reduce disease risk >5-fold, shrinks mucositis duration by 97%, has a positive Glasziou treatment effect that is 67.8-fold greater than expected, has a dose–gradient response, and accomplished this in a diverse and heterogeneous clinical settings containing some elements that can mask a positive treatment effect. Conducting RCT on HPPCLS, while eventually necessary, would be redundant to assess causality or strength of association.

More consequential to patient care, at this point, would be institutional evaluations of HPPCLS in cohorts of patients vulnerable to mucositis during cancer treatment.

To this end, it is suggested that HPPCLS be tested by institutional investigation of practice-based teams comprising of nurses, nurse practitioners, physician assistants partnered with oncology fellows, and/or radiation oncology residents to examine the verity of HPPCLS outcomes published to date. This data in a peer-reviewed format would provide

a preponderance of evidence that will either disprove or confirm the clinical utility of HPPCLS. As purveyors of oncology-wide practice guidelines for 97% of clinical practice, the NCCN member institutions should carry out the challenge.

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