Title:

Intravenous opioids for chemotherapy-induced severe mucositis pain in children: systematic review and single-center case series of management with patient- or nurse-controlled analgesia (PCA/NCA)

Running title:

Intravenous opioids for children with severe mucositis

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ABSTRACT

Background: Chemotherapy-induced oral mucositis can result in severe pain. Intravenous (IV) opioids are recommended, but management protocols vary. We systematically reviewed studies reporting IV opioid use for pain related to chemotherapy-induced severe oral mucositis in children, and conducted a large single center case series.

Methods: Ovid MEDLINE, PubMed and Cochrane databases were searched for studies reporting IV opioid duration and/or dose requirements for severe mucositis. Secondly, our pain service database was interrogated to describe episodes of opioid administration by patient- or nurse-controlled analgesia (PCA/NCA) for children with mucositis and cancer treatment-related pain.

Results: Seventeen studies (6 randomised trials, 2 prospective observational, 3 retrospective cohort, 6 retrospective case series) included IV opioid in 618 patients (age 0.3 to 22.3 years), but reported parameters varied. Mucositis severity and chemotherapy indication influenced IV opioid requirements, with duration ranging from 3 to 68 days and variable dose trajectories (hourly morphine or equivalent 0-97mcg/kg/hr). Our 7-year series included PCA/NCA for 364 episodes of severe mucositis (302 patients; age 0.12-17.2 years). Duration ranged from 1-107 days and dose requirements in the first 3 days from 1-110mcg/kg/hr morphine. Longer PCA/NCA duration was associated with higher initial morphine requirements (ρ=0.46[95%CI 0.35,0.57]); subsequent increased pain and need for ketamine co-analgesia (118/364 episodes with opioid/ketamine 13.9[9.8-22.2] days *vs* opioid alone 6.0[3.9-10.8] days; median[IQR]); but not with age or sex.

Conclusions: Management of severe mucositis pain can require prolonged IV opioid therapy. Individual and treatment-related variability in analgesic requirements highlight the need for regular review, titration, and management by specialist services.

***Keywords*:** mucositis; oral mucositis; pain; opioid; morphine; ketamine; chemotherapy; child

1. INTRODUCTION

Chemotherapy-induced oral mucositis is a frequent (52-80%) and one of the most debilitating side effects of cancer treatment in children.[1-4] Immune ablation by chemotherapeutic agents is also utilized prior to hematopoietic stem cell transplantation (HSCT; stem cells from blood or bone marrow) in treatment protocols for malignant or non-malignant conditions (e.g. genetic, immunodeficiency, autoimmune disorders).[5-10] Rapid turnover cells in the gastrointestinal mucosa are susceptible to anti-neoplastic drugs, and oral erythema and ulceration results in pain and difficulty swallowing, while more generalized gastrointestinal involvement can be associated with abdominal pain, diarrhea and inability to absorb oral medications or nutrients.[11]

Recent guidelines cover a wide range of topical and systemic interventions that may have preventive or therapeutic benefit for chemotherapy-induced mucositis.[11,12] Regular oral care using multi-agent topical protocols is recommended,[13] and there are varying levels of evidence for antiseptic or anti-inflammatory mouthwash, photobiomodulation, cryotherapy, coating agents, growth factors and natural therapies such as honey.[11,14-17] Pain relief is an acknowledged key element of care,[11] and intravenous (IV) opioids are required for severe mucositis when oral therapies and medications are no longer tolerated and/or provide inadequate analgesia. Recommendations for specific opioid regimens in children are hampered by the limited quantity and quality of current pediatric evidence.[13] A recent Cochrane review on tumor-related pain identified no eligible trials from which to make conclusions regarding the efficacy or harm associated with opioid treatment,[18] despite treatment-related pain (i.e. mucositis, nerve injury related to chemotherapy or radiotherapy, operative and procedural interventions) being a major concern for children with cancer. Intravenous opioids play an important role in pediatric perioperative pain management, with recommendations and guidelines highlighting the need for regular pain assessment, titration against individual response, monitoring, and management of side-effects.[2,19,20] In many centers, this experience has informed protocols for management of severe oral mucositis by inpatient pain services.[21-23]

This manuscript focusses on the use of IV opioids by intermittent bolus and/or continuous infusion for pain related to chemotherapy-induced severe oral mucositis in children. Firstly, a systematic review was conducted to summarize available data for the duration and/or dose requirements of IV opioids. Secondly, we retrieved data from 7 years of consecutive cases of mucositis managed with patient-controlled or nurse-controlled analgesia (PCA/NCA) by the pediatric inpatient pain service to describe, and explore factors associated with, the duration of opioid therapy.

2. MATERIALS AND METHODS

2.1 Systematic Review

Search terms for Ovid MEDLINE and PubMed included ("mucositis"[MeSH Terms] OR "mucositis"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] AND ("pain"[MeSH Terms] OR "pain"[All Fields]), with additional searches more specifically including "analgesia"[MESH Terms] OR "analgesic, opioids"[MESH Terms] OR "opioids"[All Fields]. Searches were conducted in December 2018 and updated in April 2021, for articles published from January 1981 to March 2021. The Cochrane Database of Systematic Reviews was also searched. A PRISMA 2020 Flowchart[24] summarizes numbers of screened abstracts, full reports assessed, exclusions and included manuscripts (review by ELS and/or SMW with discrepancies discussed and agreed). Topical morphine is suggested for adults with mucositis,[11] but evidence in children is limited,[13] and this review focused on IV administration for severe mucositis. Studies eligible for inclusion described the duration and/or dose of intravenous opioid in children with severe mucositis following chemotherapy for tumor management or hematopoietic stem cell transplantation (HSCT). Indicators of mucositis severity were noted, including use of grading tools, such as the World Health Organization Oral Toxicity Scale (OM WHO), the National Cancer Institute's Common Toxicity Criteria (NCI CTC) or the Children's International Mucositis Evaluation Scale (ChIMES)(Table 1_SuppInfo).[25,26] Study characteristics, demographic data, indication for chemotherapy, and all available details for opioid type, delivery, duration, dose and side-effects were extracted manually from the manuscripts, entered into a spreadsheet and checked (ELS, SMW). Authors were not

contacted for additional or missing data. A PRISMA checklist is included in Supporting Information (Appendix 1_SuppInfo).

2.2 Single Center Case Series

2.2.1 Project Approval

A Clinical Audit/Service Evaluation Notification Form was submitted, and the project was approved and registered by the Great Ormond Street Hospital Clinical Audit Department (Audit Reference Number: 2694). A Clinical Audit Completion Summary was submitted and acknowledged by the Clinical Audit Manager on April 1st 2021. See Appendix 2_SuppInfo for STROBE (Strengthening Reporting of Observational Studies in Epidemiology)[27] checklist.

2.2.1 Data Extraction

The Great Ormond Street Hospital (GOSH) Inpatient Pain Service manages approximately 2000 patient episodes with 10,000 consultations each year, including all surgical and medical inpatients requiring PCA or NCA. As previously described,[21,28,29] we maintained a service specific database (Microsoft SQL Server Management Studio, 2005) of all consecutive inpatient pain management episodes until these data became part of a hospital-wide electronic medical record in 2019. Data were prospectively collected at the bedside by Pain Service Clinical Nurse Specialists, and entered into the database directly via handheld tablet computers. The data entry application included various logic checks to ensure accuracy and completion of information entered. Data included: patient demographics (age, weight, sex); indication for therapy; medication and administration technique (intermittent bolus, infusion and delivery mode); initial and subsequent programming of intravenous delivery methods via patient-controlled analgesia (PCA) or nurse-controlled analgesia (NCA); analgesic technique commencement and cessation (date and time); daily dose requirements (converted into daily average mcg/kg/hr requirements here); side-effects (pruritus, nausea and vomiting, sedation, respiratory depression) and use of adjuvant therapies. At the end of treatment episodes, Pain Service staff recorded overall satisfaction with treatment (reported either by the patient, carer or nurse).

The database was interrogated (by MAJ) using Structured Query Language (Microsoft SQL Server Management Studio) queries to identify all patients with at least one PCA/NCA episode between January 2012 and December 2018 with a code indicating mucositis and/or any free text comments indicating mucositis. For these patients, data on all PCA/NCA episodes were extracted, including those before and after their episode(s) coded as mucositis. This retrieved all episodes of pain service management, and therefore included results for the same cohort of patients requiring IV PCA/NCA opioids for surgery or disease-related complications within the time period of the audit. Further data cleaning was performed in 'R' (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/) MAJ before being transferred as Excel spreadsheets to SMW. Pseudonymised data was imported into SPSS V24 (IBM®). Episodes coded separately due to a change in technique on the same day (e.g. from PCA to NCA) were identified, and duration of IV PCA/NCA opioid combined to reflect each Pain Service management episode. Hospital electronic medical records (Patient Information Management System, PiMS; NHS Digital) were accessed for clarification of the underlying diagnosis.

2.2.2 Mucositis Management and Pain Service Protocols

At GOSH, severity of mucositis is graded with an Oral Assessment Guide (modified from Eilers et al, 1988[30]; 8 items scored between 1 for normal and 3 for severe; Table 2_SuppInfo). Mouth care is managed and supervised by oncology ward teams, with parent and/or patient education and involvement as appropriate for the patient's age and clinical condition. As symptoms develop, oral mouth scores increase (pain assessment introduced once above normal value of 8/24) and oral opioids (morphine solution 5mg/ml) are commenced on a four-hourly as required schedule. At GOSH, all ward bolus and/or continuous IV opioid infusions are set-up as PCA/NCA and managed by the Inpatient Pain Service, and patients with severe mucositis are referred when oral morphine is inadequate and/or is not tolerated due to difficulty swallowing or limited absorption. Higher oral mouth scores at the commencement of PCA/NCA (often in range 12-16 due to moderate-severe scores in one or more

domains) reflect increasing degrees of mucosal damage (ulceration, sloughing, bleeding), difficulty swallowing, and/or voice changes.

For the Pain Service, episodes of care for inpatients (i.e. patients admitted to hospital requiring 24-hr care) commence on referral by ward or intensive care staff for assessment and management of both acute and chronic pain conditions, and cease when patients are transferred back to care by ward staff (e.g. pain resolved or can be managed with oral regimens) or are discharged from hospital. Following referral, patients are assessed by Pain Service medical and/or nursing staff, and IV opioids are commenced with our usual PCA or NCA protocols,[21] depending on the patient's age, cognitive ability, clinical condition, prior experience, and preference. In this manuscript, episodes of intravenous PCA/NCA begin when the device is connected and cease when analgesic requirements have reduced and intravenous opioid is no longer required, or the patient is transferred to a continuous opioid infusion during an intensive care admission. Morphine is the most common first-line IV agent (solution 20mcg/kg/ml; maximum 1mg/ml for patients >50kg; bolus 1ml), and the initial background infusion rate (0.2-0.5mls/hr; see also Table 3_SuppInfo[21]) is adjusted to match current oral opioid requirements. Fentanyl (solution 0.5mcg/kg/ml; maximum 25mcg/ml for patients >50kg) or oxycodone (solution 20mcg/kg/ml; maximum 1mg/ml for patients >50kg) are used as alternative parenteral opioids when indicated (e.g. side-effects with morphine, renal dysfunction, opioid rotation during prolonged episodes). Patients are reviewed daily (Monday-Saturday) and additionally on request by members of the Inpatient Pain Service, and after-hours by anesthesia registrars who receive a hand-over and suggested management plans from Pain Team staff. Settings are adjusted as needed; such as increased bolus size for incident pain and use prior to cares (e.g. mouth care, nappy changes, positioning) and/or increased background infusion for continuous or unpredictable pain related to more generalized gastrointestinal involvement or complications. If analgesia is inadequate or patients experience dose-limiting side-effects with IV opioids alone, racemic ketamine is added to the opioid syringe (initial 20mcg/kg/ml to maximum 1mg/ml for patients >50kg; double strength if further escalation required) with the same programming parameters, as previously described[21] (see Table 3_SuppInfo). Hourly observations by ward nursing staff

during PCA/NCA with or without background infusions include: bolus use (demands and delivered); syringe volume; pain scores (using FLACC, Wong-Baker Faces, or 0-10 numerical rating scale as appropriate for patient age and cognitive level); heart rate; respiratory rate; sedation scores (0=awake/alert, 1=sleepy/responds appropriately, 2=somnolent/rousable, 3=deep sleep/rousable with more intense stimulus, 4=unrousable) . Continuous monitoring includes pulse oximetry. Vomiting, and itch are recorded, but specific relationships with opioid intake can be confounded by clinical status, routine use of anti-emetics to minimize chemotherapy side-effects, and itch related to graft-versus-host disease.

Twenty-four hour analgesic requirements are assessed at each review. As muscositis symptoms, pain and bolus requirements decrease, a stepwise approach is used to adjust programming based on the individual's PCA/NCA settings and pattern of incident and/or continuous pain. This incorporates: reduction in bolus dose back to usual protocol (i.e. 1mL; 20mcg/kg morphine equivalent) if higher volumes had previously been required for incident pain; gradual reduction and cessation of background infusion as continuous pain and opioid requirements decrease; period of bolus only administration until the patient is tolerating oral intake/medications and analgesic requirements have reduced to a level that can be managed by usual oral opioid ward protocols (e.g. 200mcg/kg oral morphine as required 4hrly).

Detailed GOSH Pain Service protocols are available online (https://www.gosh.nhs.uk/wards-and-departments/departments/clinical-specialties/pain-control-service-information-parents-and-visitors/download-documentation/).

2.3 Statistical Analyses

As numerical data from the case series was not normally distributed (D'Agostino & Pearson test), median [interquartile range] and (range) are reported, and analyzed with Mann-Whitney or Kruskal-Wallis comparisons. Categorical data are presented as n (%). Bivariate correlations are reported as two-tailed Spearman's rho with bias corrected 95% confidence intervals (CI). Duration of IV opioid for mucositis was compared across diagnostic groups, and with other indications for IV therapy in the same patients (Kruskall Wallis). Relationships between duration of IV opioid and patient age and subsequent

requirement for ketamine, and between patient age and initial dose requirements were explored (Linear regression). Throughout, group values and analyses are based on available data, and any missing data is reflected by the reduced sample size. Analysis was performed with SPPS Statistics V27, (IBM, Portsmouth, UK; June 2020), and data plotted with Prism V9 (GraphPad, San Diego, USA; October 2020).

3. RESULTS

3.1 Literature Search

3.1.1 Study Characteristics

Following searches and removal of duplicates, 343 abstracts were screened and 66 full reports were assessed for eligibility (Figure 1). Excluded studies were: reviews without original data,[31,32] single case reports,[33] data for degree and/or duration of IV opioid was not included, or the proportion of children requiring IV opioid analgesia was reported without specific details of the duration or dose,[34-38] or opioid was administered by an alternative route (e.g. intranasal[39] or topical[40])(Figure 1). Seventeen articles (6 RCTs, 2 prospective observational studies, 3 retrospective cohort studies, 6 retrospective case series) fulfilled inclusion criteria and reported the duration and/or dose of IV opioid in children with severe mucositis following chemotherapy for tumor management or HSCT.[21-23,41-54]

Three randomized trials compared dose requirements for different IV opioids[43,50] or delivery methods.[49] Three randomized trials,[47,48,52] and one prospective observational study[41] reported opioid requirement as an outcome for efficacy of mucositis interventions.

The remaining 10 studies were observational cohorts or case series with retrospective chart or database review that provided feasibility data,[46] compared different populations[23,51] or opioids,[54] or analgesic adjuvant agents,[21,22] or correlated analgesic requirement with other outcomes/interventions[42,44,45,53] (Table 1). The variable methodology and quality of included studies (Appendix 3_SuppInfo) limited quantitative analysis.

3.1.2 Populations

Intravenous opioid duration and/or dose requirements for the management of mucositis were reported in 618 children in total; with 2 studies reporting repeated episodes in some children.[22,54] Parameters for reporting patient age varied. Ages ranged from 0.3 to 22.3 years in 11/17 studies;[21,23,44-51] mean/median from 3.4 to 15.3 years;[22,45,48,50 21,23,41-44,47,49,51,54] with a combined weighted mean of 10.9 years.[21-23,41,42,44,45,47-51,54] The proportion of males ranged from 45 - 64% in 14/17 studies (total 325/576; Table 1).

Reporting and details of underlying diagnoses varied across studies, and while one study compared different chemotherapy regimens in patients with neuroblastoma,[45] the remaining 16 studies included patients with a number of different hematological[41,43,48] and/or solid tumors.[22,23,47,51-54] Chemotherapy indications included: cancer therapy[21,22,41,48,50,52,54] and/or preconditioning for HSCT (approximately 63%); for the latter the majority were for malignancy,[23,41-47,49,51,53] with a smaller proportion (<10%) for non-malignant (e.g. aplastic anemia, metabolic disorders[21,23,42,44,47,51]) conditions (Table 1).

Mucositis was reported as severe in 15/17 studies, and requirement for IV opioid was specifically reported as an indicator of severity in 5 studies.[43,45,49,50,52]. Mucositis symptoms and signs were graded in 8 studies,[42,47,48,50-54] most commonly with the WHO tool (5 studies)(Table 1; Table 1_SuppInfo for details). Nine studies[21,22,41,43,47,49-51,54] reported pain scores using different observer tools (FLACC[21,54]); pictorial self-report (Faces scales,[47,54] Oucher[51]), numerical self-report,[21,41,47,49,50,54] or a categorial rating scale,[22] depending on the patient's age. Scores included moderate to severe pain intensity (eg. >/= 4/10) in 8/9 studies.[21,22,41,43,47,50,51,54] (Table 1).

3.1.3 Opioid regimens

Thirteen studies (3 RCTs, 1 observational, 10 retrospective) reported IV administration by: patient (PCA);[41-43,45,46,49,50,53,54] PCA or nurse (NCA);[21,22,44] or PCA or proxy/caregiver controlled (ProxyCA)[23] analgesia (Table 1). Two studies reported IV opioid bolus dose and/or infusion but no details of who administered the bolus,[47,51] and 2 studies did not include IV administration protocols.[48,52] Compared to continuous infusion of opioid, PCA was associated with similar pain scores but a lower cumulative opioid

dose in children (mean hourly morphine PCA *vs* continuous infusion: 40.5 mcg/kg/hr *vs* 72.5mcg/kg/hr)[49] (Table 1).

Thirteen studies (4 RCTs, 2 prospective observational, 6 retrospective) reported type of opioid used, and all included morphine.[21-23,41,43,44,46-51,54] Alternative opioids included hydromorphone,[23,43,46] fentanyl,[23,51,54] oxycodone,[44,47] diamorphine,[44] and pethidine.[50] Side-effects of morphine or renal impairment were reported as reasons for rotation to hydromorphone or fentanyl.[46,51] Controlled studies reported comparable analgesia with morphine and hydromorphone[43] or pethidine.[50] Two studies added ketamine to morphine PCA/NCA[21,22] and one study reported use of IV tramadol, with intermittent bolus morphine for rescue analgesia or transfer to PCA morphine or fentanyl if pain control was inadequate.[54]

Initial PCA/NCA settings varied across studies (Table 3_SuppInfo). The need for regular review and adjustment of PCA/NCA programming throughout mucositis episodes was highlighted in 5 studies.[21,22,46,51,53]

3.1.3 Duration of intravenous opioid

Duration of IV opioid was included in 16/17 studies, but reporting parameters varied (Table 1). Eight studies (4 controlled,[47,48,50,52] 4 retrospective[23,42,45,53]) explored relationships between clinical factors and duration.

Total duration of IV opioid was reported in 10 studies,[21,23,42,43,45,46,48,50,52,53] with maximums ranging from 5 to 68 days[45,47,48] (Table 1). Reported mean/median durations varied from 5 to 40 days (combined weighted mean: 13.2 days[21,23,42,45-47,53])(Table 1).

The duration of IV opioids was prolonged in patients with more severe mucositis (moderate versus severe, 5 vs 13 days[47]; all patients versus Grade III-IV, 8 vs 15 days[53]). The type of chemotherapy influenced the duration of IV opioids in patients undergoing HSCT (reduced intensity vs myeloablative conditioning; 7 vs 18 days[42]) and in patients with high-risk neuroblastoma (busulfan/melphalan vs carboplatin/etoposide/melphalan median (range); 7(1-43) vs 16(3-68) days[45]). Younger children undergoing HSCT required IV opioid for longer periods (<6 years vs 6-12 years, 40±75 vs 25±28 days).[23] Oral cryotherapy during infusions did not influence opioid duration, but compliance was limited in young

children.[47] Palifermin, a human recombinant keratinocyte growth factor that stimulates growth of new epithelial cells, did not significantly reduce IV opioid duration in patients with severe oral mucositis (16.8±9.2 vs 14±8.8 days)[53] or in patients treated for acute lymphatic leukemia (ALL; 5 vs 6 days).[48] Duration did not differ in RCTs comparing PCA morphine versus pethidine,[50] or total parenteral nutrition versus IV fluids.[52] (Table 1).

3.1.4 Opioid dose requirements

Opioid dose requirements varied widely both within and across studies, and with time in the days and weeks following chemotherapy. Hourly morphine (or morphine equivalent) doses included peak values over 70mcg/kg/hr in several studies[22,43,49,51] (Table 1). Trajectories of opioid dose demonstrated increasing requirements during initial days of therapy, with peak doses reported after five[22] or nine to twelve days of IV opioid,[44,46,49,51] followed by variable plateau periods and then gradual decreases in dose, mucositis severity and/or pain scores at variable time points from 20-30 days.[21,44,46,47,49] Three studies reported higher opioid dose requirements with increased severity of mucositis,[42,47,54] and 2 reported differences related to the type of tumor and chemotherapy protocol[23,42] (Table 1). Peak opioid requirements coincided with signs of systemic inflammation (highest CRP level also at D9-10), and occurred following the maximum enterocyte loss (lowest citrulline level at D7).[44] Reports of the impact of age on dose requirements varied across studies: no influence of sex[54] or age[44,54] in 2 pediatric studies, but higher doses in children than adults following HSCT.[51] Palifermin reduced median daily morphine requirements in patients treated for ALL.[48] There was limited data regarding total morphine exposure, but reports include a range of 0.4 to 3.3mg/kg morphine over 2 to 15 days,[50] up to 11.8mg/kg over 21 days,[44] and mean±SD of 21±23mg/kg in children under 6 years requiring 40±75 days of IV opioid therapy.[23]

Ketamine was added to IV PCA/NCA (average 4 days following commencement of IV opioid) for patients with inadequate analgesia or dose-limiting side-effects, and was reported to decrease opioid requirements and/or improve analgesia.[21,22] Ketamine co-analgesia was used in 233/860 (27%) patients,

and more frequently in females, older patients, and those with a rapid escalation of initial morphine dose (D0-D2).[22]

3.1.5 Side-effects

The reporting of side-effects, and the scales used, varied across studies. No episode of respiratory depression was specifically reported in 3 studies,[21,43,46] while cases of severe (unarousable) sedation,[54] moderate (arousable) sedation,[22,43] reduced respiratory rate,[54] drowsiness,[50] and mild-moderate degrees of trouble keeping awake[49] were reported in 5 studies (Table 1). Respiratory support, ranging from oxygen supplementation to controlled ventilation in an intensive care unit (ICU), was needed for chemotherapy-related side-effects in one study.[45] No psychomimetic side-effects or hallucinations were attributed to ketamine,[21,22] although ketamine was removed in a patient who became confused during a septic episode and required intensive care.[21]

3.2 CASE SERIES: SEVEN YEARS MANAGEMENT BY PAIN SERVICE

3.2.1 Demographics

From January 2012 to December 2018, the GOSH Inpatient Pain Service managed 717 episodes of intravenous opioids for chemotherapy and/or treatment-related cancer pain in 335 patients (male 203/335; 60.5%) (Table 2). Many patients required repeat episodes of IV opioid for the same and/or additional indications. Mucositis following chemotherapy was the primary indication for PCA or NCA IV opioid in 364/717 (51%) of episodes. For mucositis, PCA was utilized in 93/364 (25.5%; patient age median[IQR] 10.6[8.3-12.2] yrs) episodes, NCA in 271/364 (74.5%; age 3.1[1.5-5.4]yrs), and changes between NCA or PCA protocols withinin 32 episodes (age 7.0[5.8-10.8]yrs). At the first episode of severe mucositis, patient age ranged from 1 month to 17.4 years (median[IQR]:4.4[1.9-7.5]) and weight from 4 to 90 kg (16.6[11.7-24.7]). Additional PCA/NCA episodes related to: subsequent onset of chemotherapy-related complications (graft vs host disease or veno-occlusive disease, n=39); monoclonal antibody (anti-GD2) infusion for high-risk neuroblastoma (n=142); surgery for cancer-related management or

complications (n=120); and IV opioid for pain from other causes, medical complications, tumor relapse and/or palliative care (n=52) (Table 2).

Underlying diagnoses were grouped as: leukemia (n=109; including acute lymphoblastic leukemia, acute myeloid leukemia); lymphoma (n=31; including B-cell, T-cell, or Hodgkin's lymphoma); neuroblastoma (n=67); hemophagocytic lymphohistiocytosis (HLH, n=24); central nervous system (CNS) tumor (n=24); other solid tumor (n=23; including sarcoma, renal and rhabdoid tumors); and hematopoietic stem cell transplant (HSCT) for non-malignant conditions (n=57; including immunodeficiency and genetic conditions). Patients with solid tumors (including neuroblastoma, CNS, renal and bone tumors) were younger than patients with hematological (leukemia and lymphoma) malignancies (median[IQR]; 3.3[2.2-5.5] *vs* 6.1[3.1-9.5] years).

3.2.2 *Duration of therapy*

The duration of IV opioid PCA/NCA for 364 episodes of mucositis in 302 patients ranged from 1 to 107 days (median 8.8 [IQR 4.9-14.6])(Table 2). Duration of therapy did not differ between males and females (8.6[4.7-13.5] vs 9.0[5.7-15.1] days) or across diagnostic groups (Figure 2A,B), and was not related to patient age (Spearman's rho ρ= -0.06[95%CI -0.17,0.04]). Duration of therapy was longer in patients who required higher initial morphine doses (Figure 2C) and this correlation persisted across the first 3 days (day of commencement, D0 ρ=0.16[0.04,0.28]; D2; ρ=0.46[0.35,0.57]; Table 4_SuppInfo).

Duration of individual PCA/NCA episodes under-estimated total opioid duration in 9 patients who were transferred to continuous opioid infusions in ICU for periods of 1 to 15 days before returning to ward PCA/NCA protocols. Three episodes included alternation between IV and subcutaneous protocols during periods of restricted IV access.

3.2.3 Dose requirements

Morphine was the first line IV opioid in 330/364 (91%) mucositis episodes. Hourly morphine dose on D0 (n=310 episodes) did not differ between males and females (14.3[8.4-22.7]) vs 14.8[9.1-22.5] mcg/kg/hr; median[IQR]), or across diagnostic groups (H(6)=12.8; p=0.05, Kruskall Wallis)(Table 2). Hourly morphine

dose correlated with patient weight (ρ=0.14[0.04,0.29], p<0.05) on D0 but not subsequent days, and individual requirements from D0 to D2 were variable across all age ranges (Figure 2D-F).

Fentanyl was used as an alternative first line opioid in patients with significant renal impairment or based on previous patient experience (e.g. significant pruritis with morphine). Rotation to equianalgesic doses of other opioids (fentanyl or oxycodone) was documented in 54/364 (14.8%) episodes, most commonly in patients with limiting side-effects or during prolonged therapy. Doses of other opioids were not available for conversion to morphine equivalents.

3.2.4 *Additional analgesia*

Ketamine was added to IV opioid PCA/NCA in 32.4% episodes. The requirement for ketamine was associated with longer duration of therapy, irrespective of patient age, and with higher initial morphine requirements (Figure 2G-I). Paracetamol (acetaminophen) was administered at some time during 56% of episodes, and non-steroidal anti-inflammatory drugs (NSAIDs) were rarely used (2.7%), with both only for limited periods due to potential contra-indications (e.g. masking fever during neutropenia, gastrointestinal ulceration, thrombocytopenia, renal impairment) and following discussion between management teams (Table 2).

3.2.5 Side-effects and complications

As mucositis symptoms resolved, patient's bolus usage decreased, and PCA/NCA programming was adjusted based on daily assessments of opioid requirements and the pattern of incident and/or continuous pain. This stepwise approach avoids rapid changes in opioid dose and withdrawal symptoms were not reported. Overall satisfaction was graded at discharge from the pain service in 249 episodes: fair in 2.4%, good in 33%, and very good in 65%. Fourteen patients with significant clinical deterioration, often associated with sepsis, were transferred to ICU for respiratory, cardiovascular and/or renal support. Two patients initially managed for mucositis were transferred to the palliative care team for end-of-life care, and six patients died from disease-related complications. Separate episodes of IV PCA/NCA opioid therapy were also required for delayed episodes of treatment-related complications (e.g. graft versus host disease, GVHD or veno-occlusive disease, VOD) and disease-related complications

or other causes of pain (e.g. non-specific abdominal pain, neuropathic pain, relapse, shared care with palliative care)(Table 2).

3.2.6 PCA/NCA for additional treatment-related pain episodes

Ninety-two patients within this case series required one or more additional episodes of IV PCA/NCA for postoperative pain management following surgery for tumor resection (n=93; including excision of solid tumor via laparotomy, thoracotomy or craniotomy) or other procedures/complications (n=27; including open biopsy, laparotomy for bowel complications, splenectomy). American Society of Anesthesia (ASA) scores at the time of surgery were high (73.5% ASA 3, 5.5% ASA 4). The duration of postoperative IV opioid was much shorter than for mucositis (3.0 [1.8-4.6] vs 8.8 [4.9-14.6] days; P<0.001, Mann-Whitney)(Table 2). Postoperative morphine dose requirements were higher for surgical than mucositis episodes on D0 (22.5 [12.5-32.5] vs 14.4 [8.5-22.5] mcg/kg/hr; P<0.001, Mann-Whitney) but reduced with time. Paracetamol and NSAIDs were more commonly given during surgical episodes, and a smaller proportion required addition of ketamine to PCA/NCA (Table 2).

Monoclonal antibody directed against disialoganglioside (anti-GD2) infusions accounted for 142 PCA/NCA episodes in 55 patients with high-risk neuroblastoma (Table 2). Duration and number of episodes are determined by oncology protocols, but changes in the formulation and protocol over time have reduced opioid requirements (start year negatively correlated with D0 morphine dose, $\rho = -0.45$ [95%CI -0.62,-0.24]) and the need for ketamine (2012-2014 vs 2015-2018: 26/58 vs 15/84 episodes; χ^2 $p<0.001$).

4. DISCUSSION

Chemotherapy-induced oral mucositis in children can induce severe and prolonged pain, that requires management with intravenous opioids. A systematic review including prospective and retrospective studies, and our single center case series, identified morphine as the most common opioid with delivery by variable PCA/NCA protocols to facilitate titration against individual analgesic response.

The severity of mucositis is a key factor influencing both IV opioid duration[35,47,53,54] and dose requirements.[42,47,54] Tools that identify severe oral mucositis by grading mucosal tissue damage (e.g erythema, ulceration, fibrinous plaques, bleeding), pain and difficult swallowing, and potential life-threatening toxicity, can be used to guide oral care protocols, identify patients with increasing analgesic requirements, and assess chemotherapy-related toxicity.[25,55,56]

Pain assessment in children with severe mucositis encompasses measures of pain intensity, the site and distribution of pain, relative contributions of incident and continuous pain, aggravating and relieving factors, side-effects, and co-morbidities and complications. Several studies reported use of age-appropriate validated tools for measuring pain intensity,[21,22,41,43,47,49-51,54] but details regarding the timing and standardization of assessments are difficult to determine from retrospective series. Despite PCA/NCA, a proportion of patients continued to report moderate-severe pain scores,[41,43,47,49,50] thus highlighting the need for ongoing review and titration, as high pain scores triggered an intervention in some series (e.g. change in opioid protocol[50,54] or addition of ketamine[21,22]). Mouth care to remove debris and reduce the risk of secondary infection is an important aspect of care, but this and other local interventions such as cryotherapy,[47] may be poorly tolerated by children as the severity of mucositis and pain increases.[35] Management of incident pain with PCA/NCA bolus administration prior to cares can improve patient compliance with current and subsequent painful procedures,[57] and one study reported improvement in both incident pain and pain at rest before and after an intervention.[54] The majority of pediatric protocols also included a range of background infusion doses,[21-23,41,43,46,49] (only one study reported bolus only[50]), particularly for those with pre-existing or high opioid requirements and more generalized gastrointestinal involvement and continuous pain.[44,46]

Evidence-based recommendations for PCA/NCA in children are available for post-operative pain management,[2,19] but controlled data in children with mucositis is limited. While postoperative experience may inform initial dosing and local practice protocols for PCA/NCA, the trajectory of pain and co-morbidities associated with oral mucositis differ significantly. Following chemotherapy, analgesic requirements tend to increase over several days, reach a plateau and then gradually resolve, but there is

significant variability in opioid dose requirements and duration of therapy.[22,23,42,47,49,58,59]. As shown by comparison with the post-surgery cohort in the current and previous GOSH case series,[29] post-operative dose requirements are highest on the day of surgery, decline more quickly, are more closely related to age/weight, and use of multimodal analgesia is more frequent.

Morphine was the most commonly reported first-line opioid for PCA/NCA. In controlled comparisons, albeit with limited sample size, no difference in efficacy was found between IV PCA morphine versus hydromorphone in a cross-over study[43] or morphine versus pethidine (meperidine),[50] although the latter is no longer recommended for PCA as accumulation of the metabolite norpethidine can result in CNS toxicity.[2] Patients previous experience of opioid-related side-effects, and development of hepatic or renal dysfunction related to sepsis, GVHD or VOD, can also influence choice of opioid.[22,46] Identifying specific opioid-related side-effects can be difficult. Nausea and vomiting are common with chemotherapy, itch may be related to skin rashes with GVHD, and prophylactic anti-emetics and anti-pruritics are often part of oncology protocols.[43] In children with disease- or treatment-related cancer pain (70% due to mucositis), rotation to an alternative opioid (morphine, hydromorphone, fentanyl, pethidine) was reported in 30 of 414 (7.2%) of inpatient episodes for management of excessive side-effects, inadequate analgesia or tolerance.[60] In the more recent GOSH series, 14.8% of mucositis episodes included opioid rotation (morphine, fentanyl or oxycodone), which may reflect increasing use of this technique with time. Despite limited differences in morphine-equivalent dose, reduction in side-effects has been reported with rotation between different opioids (resolution following 27/30 rotations in 414 patients[60]), and with rotation from morphine to fentanyl (2/103 episodes[22]) or hydromorphone (10/39 patients)[46] Criteria, benefits and dose requirements for opioid rotation require further evaluation in large controlled studies. Respiratory depression was absent[21,46] or not reported in many series, but the need for respiratory support can also be influenced by tumor-related factors (e.g. abdominal distension, pulmonary edema) or treatment-related complications (e.g. sepsis).[45] As analgesic requirements tend to reduce gradually as symptoms resolve,[44,51] withdrawal symptoms that are more typically associated with rapid dose changes or acute cessation of opioids[61,62] are rare.

Ongoing or new sources of pain due to chemotherapy- or disease-related complications can extend the need for IV opioids to weeks and months. Immunocompromised and neutropenic patients following chemotherapy are at risk of bacterial, viral and fungal infections in blood, gastrointestinal, respiratory and urinary tracts,[42,52,53] and sepsis increases the need for respiratory support and intensive care management.[22,42,45,46,63] Graft versus host disease (GVHD), due to donor/graft T cells attacking host cells following allogeneic stem cell transplantation can produce gastro-intestinal symptoms (e.g. diarrhea and pain), hepatic impairment and jaundice, skin rashes and itch.[5,46] Veno-occlusive disease, also known as sinusoidal obstruction syndrome (VOD/SOS), due to obstruction of liver sinusoids by cellular debris following HSCT or specific chemotherapies such as oxaliplatin and 5-fluorouracil, can result in hepatic dysfunction and ascites, and pain from hepatic capsule or abdominal distension.[63] Some children requiring prolonged therapy in the GOSH series had progressed to GVHD or VOD/SOS within the same episode of IV opioid therapy for mucositis, but the relative contribution to pain and the timepoint of this transition could not be clearly determined.

Ketamine has been used as an adjuvant or co-analgesic when severe mucositis pain is inadequately controlled with IV opioid alone.[13,21,22] The need for ketamine has been associated with: mucositis severity and higher pain scores;[35] rapid escalation in early morphine requirements, older age and female sex;[22] high pain scores;[21] and in the current series, with higher initial morphine requirements and prolonged duration of IV PCA/NCA. While additional high-quality evidence is required to determine the risk-benefit with different doses and preparations (eg. racemic vs S-ketamine, although the latter is not available in all countries[2]), or routes of administration (eg. ketamine mouthwash[64]), the range of adjuvants suitable for children with severe mucositis is limited by the ability to tolerate oral medications and chemotherapy-associated side-effects. Neutropenia has been used as a marker of the intensity of chemotherapy, severity of mucositis and need for IV opioid analgesia,[54] and concerns about masking fever as a sign of sepsis in neutropenic patients contribute to variable use of paracetamol across series.[35] Non-steroidal anti-inflammatory agents are frequently contra-indicated by co-morbidities such as thrombocytopenia, gastro-intestinal ulceration, or renal impairment.

Survival from high-risk neuroblastoma is improved by monoclonal antibody directed against a cell surface disialoganglioside (GD2) expressed by neuroblasts.[65,66] GD2 is also expressed by nociceptive C-fibres,[67] and resultant acute neuropathic pain can be managed with gabapentin (commenced prior to treatment), supplemented with IV opioids during infusion. In our series, opioid requirements reduced with time as newer protocols were adopted, and lower requirements have also been documented with more recent preparations.[68]

While not reported in studies in the current systematic review, systemic gabapentin and clonidine have been used in a small proportion of patients with mucositis,[35] and gabapentinoids and tricyclic anti-depressants are suggested as first line agents for cancer-related neuropathic pain in children.[69] Chemotherapy-induced peripheral neuropathy and acute neuropathic pain occurs in 50-90% of children treated with platinum compounds (e.g. cisplatin) and 35-45% with vinca alkaloids (e.g. vincristine.[70-73]), but the contribution of neuropathic mechanisms to prolonged mucositis pain is unclear. The ability to recognize and manage potential dose-limiting toxicities is vital, as modification of treatment protocols may impair the recent advances in survival from pediatric cancer with newer multi-agent protocols and therapies, and reduce the potential prolonged benefit following stem cell transplants for non-malignant conditions.[9,10,58,74] Following survival from childhood cancer, 12-20% of adults reported chronic pain, 16.7% used prescription analgesics, and 21% attributed pain to cancer and treatment.[75] The impact of early life exposure to chemotherapy and pain, and the adequacy of acute pain control on long-term nociceptive processing and future pain response, requires ongoing evaluation.

This report has several limitations. The systematic review summarizes current literature of IV opioid use by bolus and/or continuous infusion for mucositis in children, but variability in study design, reporting and underlying conditions limits quantitative analysis, and the protocol was not prospectively registered. The GOSH case series retrospectively analysed data collected at the bedside during episodes of care. Clinical features and duration of IV opioid are reported for episodes of mucositis and other treatment-related conditions, but given the number of episodes, only selected data was extracted. Dose data was limited to morphine in the first 3 days and associations with subsequent duration and need for

ketamine were explored. Hourly pain scores are recorded by ward staff and are reviewed by the pain service at each visit, but were not extracted here, as the timing and relationship between incident and continuous pain is not evident from the retrospective records, and adjustments in PCA/NCA protocols are also informed by the nature of pain and discussion with patients and families. Summary data for major side effects is included, but the relative contribution of opioids versus chemotherapy to side-effects such as nausea, vomiting or pruritis could not be evaluated. However, our 7-year audit highlights the significant pain and disease burden experienced by children with cancer, and the requirement for multiple treatment episodes. While severe mucositis has significant implications for resource utilization and health care costs, a recent analysis[74] did not include costs associated with analgesia (e.g. drugs and equipment) or the staffing, expertise, and frequency of review undertaken by many services to maximise analgesia.[35]

Guidelines for the management of pain with severe mucositis are hampered by the quantity and quality of current evidence.[14] Recommendations for IV opioids in pediatric patients[13] include data from 2 randomized trials reported here,[43,49] and the pre-post evaluation with addition of ketamine.[21] The current review has included a broader range of descriptive and retrospective studies to provide a narrative summary and comparison data for our single center audit. PCA/NCA protocols for bolus and background opioid doses vary across centers, but the current literature review and case series highlight important issues for clinical practice: inter-individual and treatment-related variability in the required duration and dose of IV opioid therapy; the need for regular review and adjustment of protocols to facilitate individual titration of analgesia and minimize side-effects; requirements for expertise and adequate resources to manage complex pain following chemotherapy; and the significant co-morbidities that may also influence analgesic management in children with severe mucositis.

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CONFLICT OF INTEREST

The authors report no financial conflict of interest relevant to this manuscript. Suellen Walker is a Section Editor for *Pediatric Anesthesia.*

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Table 1. Intravenous opioid use for severe mucositis: data extraction from included studies.

Ref.	Study type. Comparison group	Sample size (% male)	Age	Mucositis grade	Analgesia & route	Dose	Duration	Pain scale	Opioid-related side-effect score or incidence (%)	Indication: diagnoses, number cases
(Alonso Puig et al., 2020)[41]	Prospective observational study. Pre and post intervention (video game distraction)	20 pts (1 excluded). 9M (45%)	Mean±SD 11.5±4.5 yrs	Severe OM	IV PCA Morphine	Daily morphine pre vs post intervention 35.9±27 vs 28.6±27.1 mcg/kg reported. Bolus per day (10mcg/kg) number 17±14.9 vs 9.5±9.5	Data for 24hrs pre and 24hrs with use of video games (2.3±1.3 hrs/day)	NRS 0-10. Pre vs post: Incident pain 7.7±2.3 vs 5.4±2.7 Pain at rest 4.8±2.8 vs 3.2±2.8	NR	Malignancy: Haematologic 15 BMT 5
(Barrell et al., 2012)[42]	Retrospective cohort with chart review. Reduced intensity conditioning (RIC) vs myeloablative conditioning (MAC)	86 pts, 55 M (64%) 43 per grp	Mean 10.4yrs	Severe OM grade >/=3 in 9/43 RIC vs 23/43 MAC	IV PCA Regimen NR	NR	Data D0 – 30. RIC vs MAC: Require PCA 33±7% vs 81±5.9% Duration 7 vs 18 days	NR	NR	HSCT: Malignant 55, non-malignant 31
(Collins et al., 1996)[43]	DB RCT with 3-period cross-over. Randomised to morphine-hydromorphine-morphine (M-H-M) or H-M-H	10 pts.	Mean 13.7 or 15.3 yrs	Severe OM requiring IV opioid. Range from D0 to D9 post Tx; all req intermittent or continuous IV opioid pre-study)	IV PCA Morphine or hydromorphone (M-H-M, or H-M-H)	Hourly ME dose Background range 10 – 97 mcg/kg/hr Bolus 20 – 130 mcg/kg	Data for 10 days. Duration PCA range 10-33 days (commence D0 to D9 after BMT)	VAS 0-10. Median 4 (range 0-10)	Vomiting, itch, sedation scales. Range from 1 (no vomiting; no itch; fully awake) to 4 (vomiting, generalized itch, asleep easily arousable). Median score 1	BMT: Haematologic cancer 10
(De Pietri et al., 2019)[44]	Retrospective case series with chart review. Correlation between opioid requirement and systemic inflammation	38 pts, 23M (61%). 31 IV opioids (oral only 5, rectal only 1)	Mean 7.6 (range 1.1 – 15.8) years	NR	IV PCA/NCA 22/31 Intermittent IV 9/31 Morphine, oxycodone, diamorphine converted to IV MEs	Daily ME dose median 140 [IQR 30-260] (range 0-610) mcg/kg/d, (0-25 mcg/kg/h) Peak Day 10: 360 [0-490]; Day 21: 20 [0-10] TOTAL ME (0-21dys): median 3.7 [2.7-6.6] (range 0-11.8) mg/kg	Data for D0 to D21 post HSCT. Morphine requirement from D0 and ongoing at D21 in some	NR	NR	HSCT: Malignant 23 [eg. ALL, AML] Benign 15 [eg. aplastic anemia, immuno-deficiency]
(Desai et al., 2016)[45]	Retrospective cohort with chart review. Carboplatin/ etoposide/ melphalan (CEM) *vs* busulfan/ melphalan (BuMel)	65 pts, 37M (57%). CEM 44, BuMel 21	Median (range) years CEM 3.4 (0.8-22.3) vs BuMel 4.2 (1.4-11.7) years	Severe OM requiring IV opioid	IV opioid (drug NR) PCA in 59/65 Intermittent or scheduled bolus in 6/65	NR	Median (range) days. CEM 16 (3-68) vs BuMel 7 (1-43) days	NR	NR Respiratory support ± ICU required for chemotherapy related complications	BMT: High-risk neuro-blastoma

(Dunbar et al., 1995)[46]	Retrospective case series with chart review. Description of PCA feasibility	39 pts, 21M (54%) Additional episode in 3.	Range 4-12 yrs	Severe OM Second episode in 3 (GVHD, infection, relapse)	IV PCA, 2 converted to CI (behavior) Morphine 38 episodes; Hydromorphone 3 episodes; Rotate M to H 10 episodes	Mean hourly morphine each day range 2-30mcg/kg/hr [upr 95%CI 38]; peak D11-12	Median 19 (range 0-36) days. 21% <10 days, 15% >30 days	NR 'titrate to patient satisfaction rather than predefined pain score'	No episodes respiratory depression or use of opioid antagonist	BMT: mucositis 69% episodes, later GVHD 18%, surgery 5%, other 8%
(James et al., 2010)[21]	Retrospective cohort with database review. Compare pre *vs* post addition of ketamine.	33 pts, 20M (61%)	Mean 5.1 yrs (range 0.3-13.6yrs)	Severe OM	IV NCA n=27; PCA n=6 Morphine + ketamine (added mean 4 days (0-6)	24hr dose pre-ketamine 33.1±10.7 mcg/kg/hr (794±257 mcg/kg/d); post ketamine 35.2±14.3 mcg/kg/h	Mean 16.8 (range 5–32) days	FLACC, Wong-Baker Faces, NRS (all 0-10). Reduced frequency pain > 4/10 post ketamine	No episodes respiratory depression, excess sedation, hallucinations. Nausea and vomiting 58%, Pruritis 44%	Malignancy: Haematologic 22, solid 5 BMT: non-malignant 6
(Kamsvåg et al., 2020)[47]	Randomised trial. Cryotherapy (cool with ice during chemo infusions) *vs* usual mouth care.	49 pts, 26M (53%) OC 26, control 23. Opioids in 38.	Mean 10.5±4.3 yrs (range 4-17)	Severe OM. WHO-OTS >/=3 in 26. Mean duration severe OM 3 days	Morphine or oxycodone, intermittent or continuous infusion (regimen NR)	ME 0 - D20 post Tx TOTAL: severe OM 8.8mg/kg vs 1.9mg/kg (proportion patients / time with oral vs IV NR)	Data for D0 – D20. Severe vs moderate OM require opioids for 13 vs 5 days	Faces Pain Scale-Revised (0-10) NRS (0-10. Mean range 2-6; peak at D8-9	NR	HSCT: Haematologic & other tumour. Non-malignant including aplastic anemia
(Lucchese et al., 2016)[48]	DB RCT. Palifermin *vs* placebo	44 pts, 24M (55%) Palifermin 24, control 22.	Median 12yrs (range 8-15)	WHO Grade. Severe OM with palifermin 17 vs 32%	Morphine (regimen NR)	Median daily morphine 140mg vs 210 mg (weight not reported)	Palifermin vs control 5 vs 6 days	NR	NR	Malignancy: ALL
(Mackie et al., 1991)[49]	Randomised trial. PCA vs continuous infusion (CI)	20 pts, 10M (50%). 10PCA, 10 CI (>/=7 days IV)	Mean±SEM PCA 13.6±0.6 yrs CI 14.8±0.5 yrs (range 12-18)	Pain not controlled by topical. Grade NR	Morphine PCA CI: loading 45mcg/kg; commence 15mcg/kg/hr	PCA vs CI Mean hourly morphine each day 40.5 mcg/kg/hr vs 72.5mcg/kg/hr TOTAL morphine at D10 4.94±0.86 vs 12.17±2.04 mg/kg Peak D9.	Data for 18 days. 7 patients ongoing IV opioids at 18 days.	VAS 0-10. Mean VAS >4/10 both groups first 9 days; PCA vs CI n.s.	Daily self-report (VAS 0-100) Nausea: mean 8-45/100; Trouble keeping awake: mean 0-35/100.	BMT: Myeloablative conditioning
(Oudot et al., 2011)[50]	DB RCT. Morphine *vs* pethidine PCA	35 pts, 20M (57%). IV PCA for >24hrs in 29 pts.	Median 14yrs (range 5-24)	Moderate-severe OM. WHO Grade 1-2 11; 3-4, 24 Require IV opioids, 30	IV PCA Morphine n=14 Pethidine PCA (5:1 dose), n=15	Total dose for D1-5 of trial. Morphine median 0.93 (range 0.37-3.33) mg/kg; pethidine 4.65 (1.35-21.9)	Morphine median 6.5 (range 2-15) days; Pethidine 5.5 (1-14) days PCA cease <5 days: resolution 3, rotate to fentanyl 7	VAS 0-10, mean 4 measures/day. D0: all >5/10 D2-D5: morphine median 4.4 (range 1.3-7.2); pethidine 3.3 (0.3-8.9)	Drowsiness 27%; Vomiting 27%; Pruritis 17%	Malignancy: Hematologic 8, solid 23, other 4
(Pederson and Parran, 1999)[51]	Prospective observational cohort.	20 pts, 10M (50%).	Mean±SD 9.9±3.5 yrs (range 5-17)	Nurse Observation Scale 0-12.	IV infusion ± bolus (details NR) Morphine, change to fentanyl in 1	Daily (D0-21) ME Range 0.09 – 1.9 mg/kg/d; 0.4 - 79mcg/kg/hr	D0 – D21 post Tx; one pt discharged at D19; ongoing morphine at D22	Oucher scale 0-10. Mean daily 1.9 – 3.5/10; peak D8	Somatic distress score (22 symptoms	BMT. Haematologic 13, solid tumour 4, aplastic anemia 3

	Opioid requirements children *vs* adults (21-54 yrs)			Daily scores range 4.3 – 7.9, peak D5		Peak D12, remain ~1.2mg/kg at D21 One pt cease at D19			including pain, vomiting, sedation) Range 33 to 43 on 0-110 scale	
(Schmid et al., 2006)[52]	Randomised trial. TPN *vs* IV fluid N/2 saline 2.5%D	30 pts.	Range 1-18yrs	Severe OM, WHO OM Scale Gd IV requiring IV analgesia	IV opioid (type, regimen NR)	NR	TPN group: median 5.8 [IQR3-10] days; IV fluids group: 6 [3.8-8.2] days	NR	NR	Malignancy: Haematologic 25, solid 5
(Vasquenza et al., 2015)[23]	Retrospective case series with chart review. PCA *vs* non-PCA; ProxyCA <6 yrs *vs* PCA >6 yrs age	35 pts with IV opioids, 19M (54%). < 6 yrs 8 pts, >6 yrs 27 pts.	Mean 11.1yrs (range 0.8-20)	NR	IV PCA/proxyCA (34/35 mucositis) morphine hydromorphone fentanyl	Total dose mean±SD < 6 yrs 21±23 mg/kg > 6 yrs 16±14 mg/kg	Mean±SD days <6 yrs 40±75 days; >6 yrs 25±28 days	NR	No respiratory depression or distress. No PCA cessation for uncontrolled side-effects	HSCT: Haematologic 17, solid tumour 13, benign disease 5
(Vitale et al., 2014)[53]	Retrospective case series with chart review. Palifermin vs usual care	58 pts, 34M (59%). Palifermin 25, no palifermin 33		Severe OM Gd III-IV subgroup (n=19; palifermin 5, control 14)	IV PCA titrated by Pain Team; drug/protocol NR	NR	Mean±SD days All patients: palifermin vs control 8.3±8.5 vs 8.8±8.4; Gd III-IV: 16.8±9.2 vs 14.0±8.8	NR	NR	HSCT: Myeloablative conditioning, haemotologic or solid tumours
(White et al., 2011)[22]	Retrospective case series with chart review. Opioid (morphine, M) *vs* morphine + ketamine (M+K)	85 pts. 103 episodes	Median [IQR] M: 7[3-14] yrs M+K: 12[6-12] yrs M+K: 13[12-14] yrs	Severe OM NCI-CTC scale Gd III-IV	IV PCA (77 episodes) NCA (23 episodes) Morphine: 68 episodes in 59 Morphine + ketamine: added 24 episodes in 19 M+K: from outset 8 episodes in 4	Median dose for 12 days M: 500mcg relatively stable, reduce from D6 M+K: rapid escalation on D2, peak D5 ~1200 [IQR 800-1800 mcg/kg/d; 33-75mcg/kg/hr]	Data for 12 days shown; ketamine start average 5 days	Categorical scale (0-3). 0 no pain, 1 mild, 2 moderate, 3 severe. Median score: pre ketamine 2; other 1	Side-effects (% of treatment days) Over sedation (difficult to rouse) 2.5%; Vomiting 4%; Pruritis 8%; Psychomimetic 0	Malignancy: haematologic 30, solid 22, other 10; HSCT: 37
(Yaffe Ornstein et al., 2020)[54]	Retrospective case series with chart review. Descriptive feasibility IV tramadol	34 pts, 17M (50%). 54 episodes (tramadol only 34; plus rescue opioid 20)	Mean±SD Tramadol: 11.3±6.9yrs Tramadol plus 12.6±6.8 yrs	Moderate to severe OM. WHO OM Scale Gd II 12 episodes; Gd III-IV 42 episodes	IV tramadol 1-2mg/kg 6hr (max 400mg/day). Rescue IV morphine 0.1mg/kg 2hr. Morphine/ fentanyl PCA (protocol NR)	Tramadol 4-8mg/kg/day (34 episodes); tramadol + 0.1-0.4 mg/kg/day morphine rescue (15 episodes); morphine/ fentanyl PCA (5 episodes)	NR	FLACC, Wong-Baker Faces, NRS (0-10). Pain score >4 on admission; >5 add rescue IV morphine; inadequate switch to PCA	Respiratory depression (RR<10) 3.7% episodes; Grade 4 sedation unarousable 0; Nausea 2%; Pruritus 0; Hallucinations 0	Malignancy: haematologic 10, solid 17; HSCT: 8

Legend: ALL, acute lymphatic leukaemia; AML, acute myeloid leukaemia, BMT, bone marrow transplant; ChIMES, Children's International Mucositis Evaluation; CI, continuous infusion; D, day; DB RCT, double blind randomised controlled trial; FLACC, Faces Legs Activity Cry Consolability pain scale; Gd, grade; HSCT, haematopoietic stem cell transplant; ME, morphine equivalent dose; NCA, nurse controlled analgesia; NCI-CTC, National Cancer Institute's Common Toxicity Criteria; NR, not reported; NRS, numerical rating scale; OM, oral mucositis; PCA, patient controlled analgesia; ProxyCA, proxy/parent controlled analgesia; pts, patients; VAS, visual analogue scale (reported as 0-10 scale); WHO scale, World Health Organisation Mucositis Scale; yrs, years

TABLE 2. Descriptive data related to 717 episodes of IV opioid use in 335 patients with treatment-related cancer pain and/or complications.

	Mucositis	**Surgery**	**Anti-GD2 infusion**	**GVHD/VOD**	**Other complications**
Demographics					
Episodes, *n*	364	120	142	39	52
Patients, *n*	302	92	55	32	35
Median Age,**years*	4.74 [2.12-7.54] (0.12 – 17.4)	4.17 [2.1-7.1] (0.11 – 14.6)	3.63 [2.96-5.83] (0.68 – 13.7)	5.59 [2.68-9.87] (0.11 – 13.4)	7.74 [4.92-9.91] (1.2 – 16.0)
Median Weight,* *kg*	17.0 [12.3-24.7] (3.5 – 78.0)	16.0 [12.0-22.7] (4.5 – 70.1)	15.5 [13.2-19.0] (6.8 – 40.0)	20.6 [12.1-30.9] (4.0 – 54.0)	23.0 [16.0-32.8] (6.0 – 89.7)
Male, *n episodes* (%) Female, *n episodes* (%)	229 M (63%) 135 F (37%)	62 M (52%) 58 F (48%)	66 M (46%) 76 F (54%	21 M (54%) 18 F (46%)	32 M (62%) 20 F (38.5%)
Diagnostic Group, *n episodes* (%)					
Leukaemia	127 (35%)	8 (6.7%)	-	23 (59.0%)	17 (32.7%)
Lymphoma	46 (12.6%)	4 (3.3%)	-	4 (10.3%)	-
Neuroblastoma	61 (16.7%)	61 (50.8%)	142 (100.0%)	6 (15.4%)	10 (19.2%)
CNS tumour	28 (7.7%)	20 (16.7%)	-	-	4 (7.7%)
Other solid tumour	24 (6.6%)	14 (11.7%)	-	-	1 (1.9%)
HLH	23 (6.3%)	4 (3.3%)	-	3 (7.7%)	3 (5.8%)
HSCT (non-malignant)	55 (15.1%)	9 (7.5%)	-	3 (7.7%)	17 (32.7%)
PCA/NCA episodes, *n*					
1	251 (69.0%)	57 (47.5%)	11 (7.7%)	12 (30.8%)	4 (7.7%)
2	81 (22.3%)	30 (25.0%)	20 (14.1%)	16 (41.0%)	16 (30.8%)
3	20 (5.5%)	12 (10.0%)	35 (24.6%)	6 (15.4%)	17 (32.7%)
4	7 (1.9%)	7 (5.8%)	30 (21.1%)	3 (7.7%)	4 (7.7%)
>/=5	5 (1.4%)	14 (11.7%)	46 (32.4%)	2 (5.1%)	11 (21.2%)
Duration PCA/NCA per episode (days)	8.8 [4.9-14.6] (1 – 107)	3.0 [1.8-4.6] (1 – 14)	4.3 [2.2-5.1] (1 – 14)	10.1 [4.8-14.6] (1 – 74)	8.3 [2.5-17.7] (1 – 94)
Morphine first line opioid, *n episodes*	330 (90.7%)	89 (74.2%)	120 (84.5%)	33 (84.6%)	37 (71.2%)
Morphine average hourly dose (mcg/kg/hr)					
Day 0 morphine *n*=episodes with available data	14.4 [8.5-22.5] (1.3 – 110) *n*=310	22.5 [12.5-32.5] (1.3 – 82.4) *n*=84	14.9 [9.7-21.3] (1.1 – 112) *n*=111	16.9 [10.6-26.1] (1.0 – 60.8) *n*=30	21.8 [6.5-34.3] (3.3 – 82.6) *n*=29
Day 1 morphine	15.8 [9.0-23.9] (0.8 – 95) *n*=307	17.0 [10.5-29.8] (0.9 – 190) *n*=80	8.6 [4.9-16.7] (0.8 – 83) *n*=107	16.3 [9.0–26.6] (1.7 – 71) *n*=29	17.2 [6.3-32.2] (0.8 – 172) *n*=29
Day 2 morphine	15.6 [9.2-25.2] (0.8 – 109) *n*=286	11.2 [5.3-24.9] (0.3 – 135) *n*=57	8.0 [3.3-14.1] (0.8 – 43) *n*=88	16.9 [5.8-28.7] (1.7 – 52) *n*=24	11.0 [4.5-22.5] (1.4 – 40) *n*=28
Ketamine added, *n episodes*	118 (32.4%)	20 (16.7%)	41 (28.9%)	12 (30.8%)	23 (44.2%)
Paracetamol, *n episodes*	205 (56.3%)	84 (70%)	79 (55.6%)	26 (66.7%)	27 (51.9%)
NSAID, *n episodes*	10 (2.7%)	22 (18.3%)	30 (21.1%)	0	2 (3.8%)

Legend: Data presented as median [IQR] (range) or n (%); *age and weight data relate to values at the beginning of each episode; morphine dose is average hourly dose across hours of therapy on day 0 (commence PCA/NCA), day 1 and day 2; CNS, central nervous system; GVHD/VOD, graft versus host disease or veno-occlusive disease as indication at commencement of NCA/PCA; HLH, haemophagocytic lymphohistiocytosis, HSCT, haematopoietic stem cell transplant

FIGURE LEGENDS

Figure 1. PRISMA 2020 flow diagram for systematic review (http://www.prisma-statement.org/)

Figure 2. Intravenous opioid requirements for severe mucositis during 364 episodes of PCA/NCA in 302 patients from GOSH case series.

A: Duration of IV PCA/NCA analgesia for episodes of mucositis (n=364) was not related to patient age (R= -0.03, $F_{1,362}$=0.3, p=0.6; n=364). B: Duration of IV PCA/NCA did not differ across diagnostic groups (H(6)=5.1; p=0.5; Kruskal-Wallis). C: Longer duration of therapy was related to higher morphine requirements on day 2 (R=0.2, $F_{1,293}$=10.2, p=0.002; n=295). Duration did not differ in cases with and without D2 morphine data (8.8[5.2-14],n=286 and 8.8[1.9,16.1],n=78). D-E: Average hourly morphine requirement for each individual patient (total dose in 24 hrs/number of hours) is plotted against patient age on initiation of IV NCA/PCA (D: Day 0; R= 0.3, $F_{1,316}$=17, p<0.001; n=318) and subsequent days (E: Day 1, R= 0.1, $F_{1,311}$=4.9, p=0.03; n=313; F: Day 2, R=0.1, $F_{1,293}$=4.4, p=0.04; n=295). Individual variability in dose requirements is evident at all ages. G: Duration of IV PCA/NCA was longer in patients who subsequently required ketamine (opioid + ketamine; n=118) versus those managed with opioid alone (n=246) (13.9[9.8-22.2] vs 6.0[3.9-10.8] days, p<0.001; Mann-Whitney). H: Duration of IV PCA/NCA was not related to age in either the opioid alone (R=0.04, $F_{1,244}$=0.4, p=0.5) or opiod + ketamine group (R=0.09, $F_{1,11}$6=0.9, p=0.3). I: Morphine requirements (average hourly dose in mcg/kg/hr on Day 0, 1 and 2) during the initial days of therapy were higher in patients who subsequently required ketamine. There was a significant effect of group ($F_{1,316}$=82, p<0.001), time ($F_{2,581}$ =5.7, p=0.004) and time x group interaction ($F_{2,581}$=4.9, p=0.008]; mixed-effects ANOVA with group and repeated measures of time as variables; no ketamine (opioid alone) n=195-220, ketamine (opioid+ketamine), n=90-93. Data = box and whiskers [5-95 percentile]. A-H: Data points = individual values; A,C,D-F,H: Lines = linear regression with 95%CI; B,G: Lines = median[IQR]; I: Data = box and whiskers with 95%CI.

Figure 1.

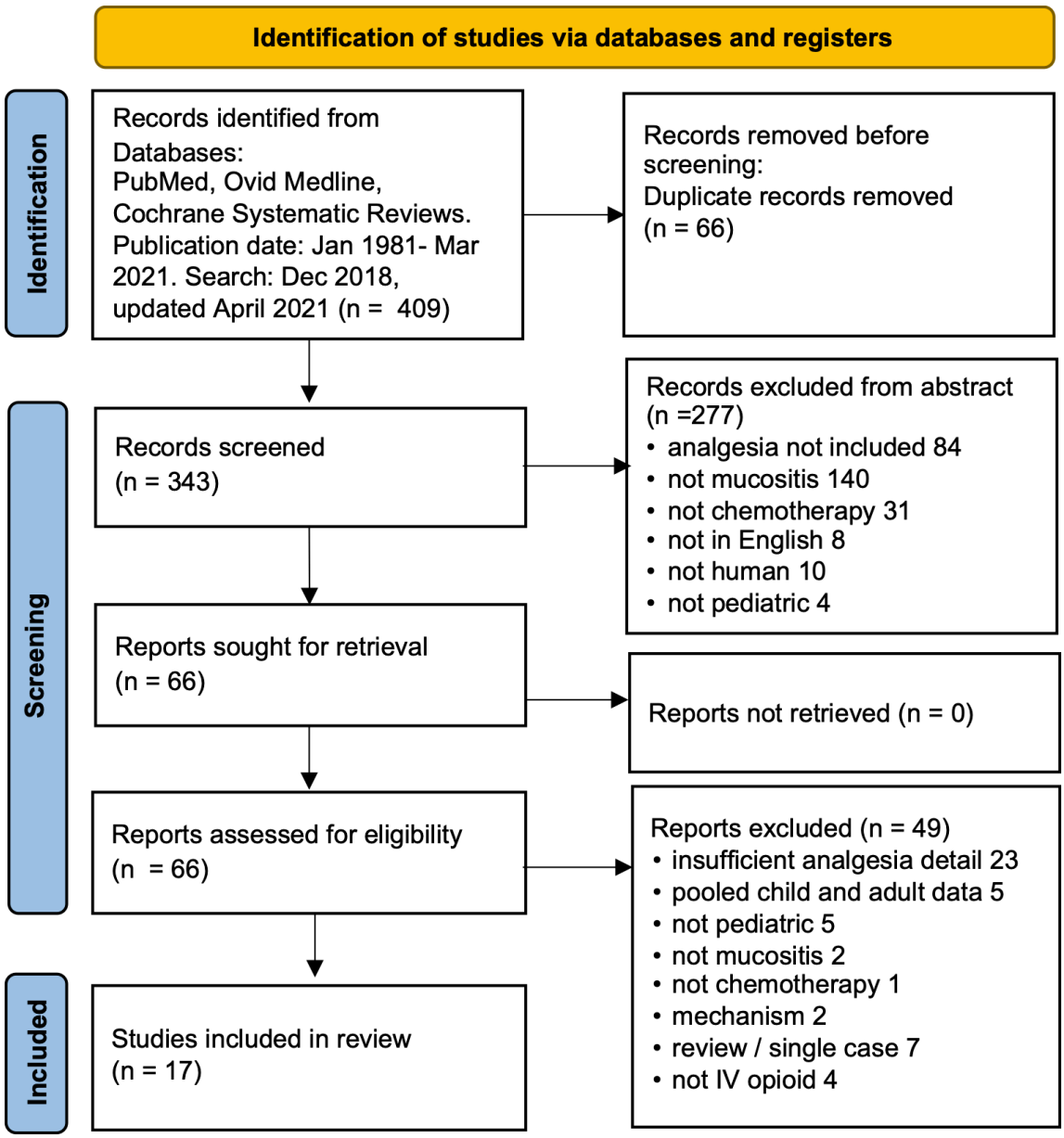

Identification of studies via databases and registers
Identification
Records identified from Databases: PubMed, Ovid Medline, Cochrane Systematic Reviews. Publication date: Jan 1981- Mar 2021. Search: Dec 2018, updated April 2021 (n = 409)
Records removed before screening: Duplicate records removed (n = 66)
Screening
Records screened (n = 343)
Records excluded from abstract (n =277)
• analgesia not included 84
• not mucositis 140
• not chemotherapy 31
• not in English 8
• not human 10
• not pediatric 4
Reports sought for retrieval (n = 66)
Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 66)
Reports excluded (n = 49)
• insufficient analgesia detail 23
• pooled child and adult data 5
• not pediatric 5
• not mucositis 2
• not chemotherapy 1
• mechanism 2
• review / single case 7
• not IV opioid 4
Included
Studies included in review (n = 17)

Figure 2

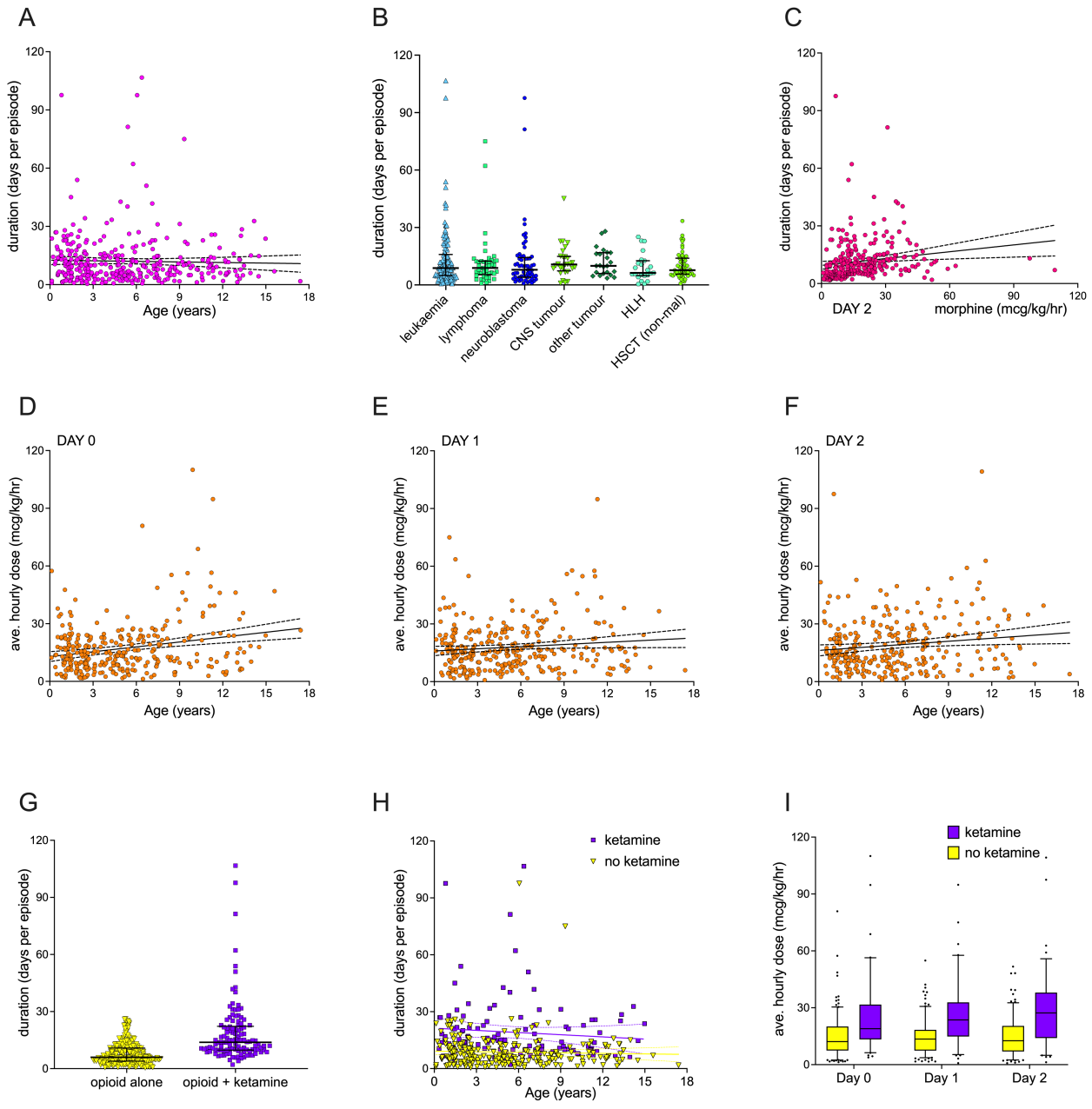

A
duration (days per episode)
Age (years)
B
duration (days per episode)
leukaemia
lymphoma
neuroblastoma
CNS tumour
other tumour
HLH
HSCT (non-mal)
C
duration (days per episode)
DAY 2
morphine (mcg/kg/hr)
D
DAY 0
ave. hourly dose (mcg/kg/hr)
Age (years)
E
DAY 1
ave. hourly dose (mcg/kg/hr)
Age (years)
F
DAY 2
ave. hourly dose (mcg/kg/hr)
Age (years)
G
duration (days per episode)
opioid alone
opioid + ketamine
H
ketamine
no ketamine
duration (days per episode)
Age (years)
I
ketamine
no ketamine
ave. hourly dose (mcg/kg/hr)
Day 0
Day 1
Day 2

TABLE 1_SuppInfo Assessment of severity of mucositis

A: Mucositis Scales

Comparison of Toxicity Grading of Oral Mucositis According to World Health Organization Criteria, National Cancer Institute—Common Toxicity Criteria, and Radiation Therapy Oncology Group Scales and Subscales

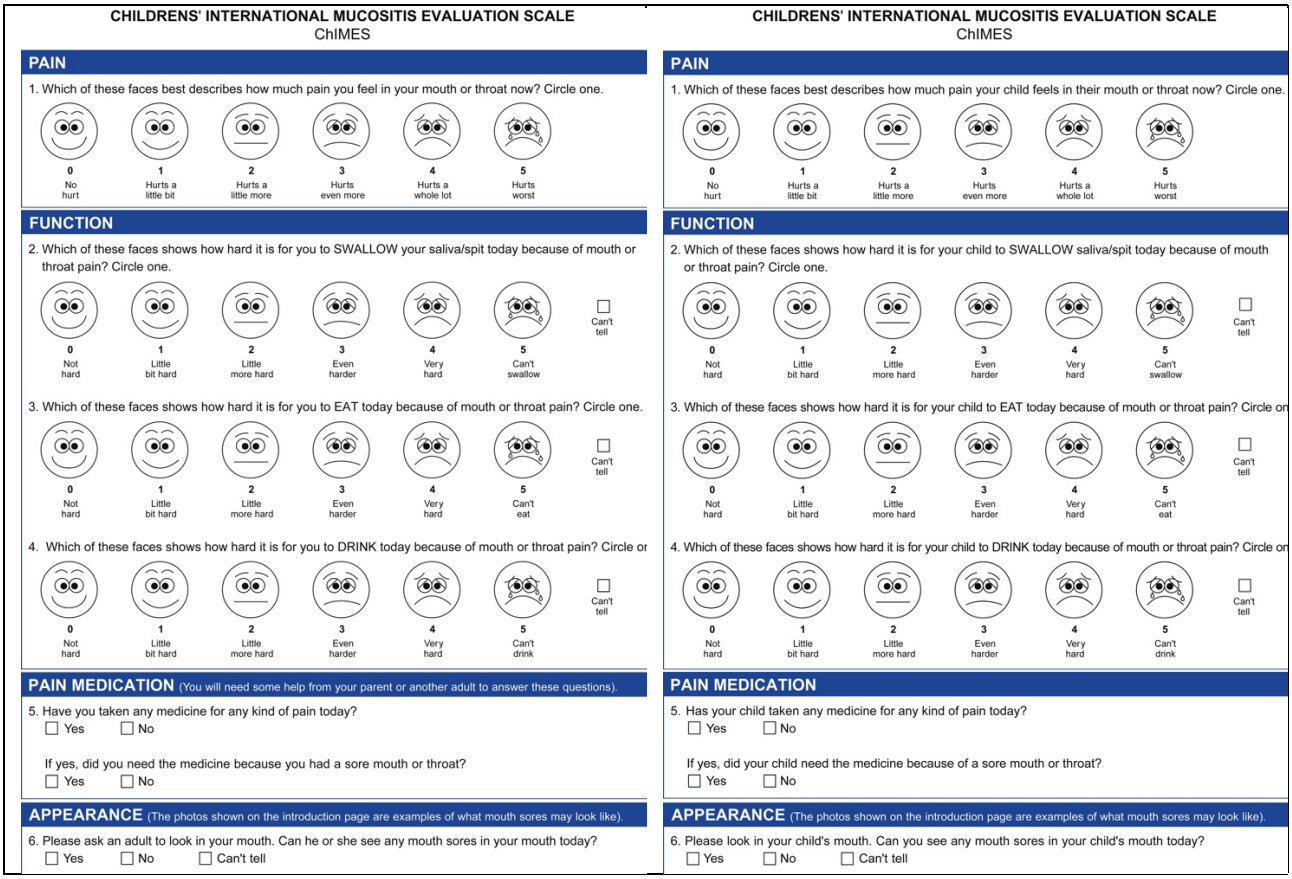
Scale	Side effect(s)	Grade 0 (none)	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life-threatening)	Grade 5 (death)
WHO	Oral mucositis (stomatitis)	None	Oral soreness, erythema	Oral erythema, ulcers, solid diet tolerated	Oral ulcers, liquid diet only	Oral alimentation impossible	—
NCI-CTC	Chemotherapy-induced stomatitis/pharyngitis (oral/pharyngeal mucositis)	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers but eating or or swallowing possible	Painful erythema, edema, or ulcers requiring IV hydration	Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation	Death related to toxicity
NCI-CTC	Associated with HSCT (stomatitis/pharyngitis, oral/pharyngeal mucositis)	None	Painless ulcers, erythema, or mild soreness in the absence of lesions	Painful erythema, edema, or ulcers but swallowing possible	Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia	Death related to toxicity
NCI-CTC	Mucositis due to radiation	None	Erythema of the mucosa	Patchy, pseudomembranous reaction (patches generally < 1.5 cm in greatest dimension and noncontiguous)	Pseudo-membranous reaction (contiguous patches generally > 1.5 cm in greatest dimension)	Ulceration and occasional bleeding not induced by minor trauma or abrasion	Death related to toxicity
RTOG	Acute oral mucous membrane toxicity caused by radiation	No change over baseline	Injection, may experience mild pain not requiring analgesic	Patchy mucositis that may produce inflammatory serosanguinitis discharge; may experience moderate pain requiring analgesia	Confluent, fibrinous mucositis, may include severe pain requiring narcotic	Ulceration, hemorrhage, or necrosis	—

WHO: World Health Organization; NCI-CTC: National Cancer Institute Common Toxicity Criteria; IV: intravenous; HSCT: hematopoietic stem cell transplantation; RTOG: Radiation Therapy Oncology Group.

From: Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer.* 2004;100(9 Suppl):1995-2025.
Reproduced with Permission. Licence No: 5110830963457; July 16, 2021; John Wiley & Sons

B: Children's International Mucositis Evaluation Scale (ChIMES)

i) Child Version	ii) Parent Version



CHILDRENS' INTERNATIONAL MUCOSITIS EVALUATION SCALE
ChIMES

PAIN

1. Which of these faces best describes how much pain you feel in your mouth or throat now? Circle one.

0 No hurt · 1 Hurts a little bit · 2 Hurts a little more · 3 Hurts even more · 4 Hurts a whole lot · 5 Hurts worst

FUNCTION

2. Which of these faces shows how hard it is for you to SWALLOW your saliva/spit today because of mouth or throat pain? Circle one.

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't swallow · ☐ Can't tell

3. Which of these faces shows how hard it is for you to EAT today because of mouth or throat pain? Circle one.

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't eat · ☐ Can't tell

4. Which of these faces shows how hard it is for you to DRINK today because of mouth or throat pain? Circle or

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't drink · ☐ Can't tell

PAIN MEDICATION (You will need some help from your parent or another adult to answer these questions).

5. Have you taken any medicine for any kind of pain today?
☐ Yes ☐ No

If yes, did you need the medicine because you had a sore mouth or throat?
☐ Yes ☐ No

APPEARANCE (The photos shown on the introduction page are examples of what mouth sores may look like).

6. Please ask an adult to look in your mouth. Can he or she see any mouth sores in your mouth today?
☐ Yes ☐ No ☐ Can't tell

CHILDRENS' INTERNATIONAL MUCOSITIS EVALUATION SCALE
ChIMES

PAIN

1. Which of these faces best describes how much pain your child feels in their mouth or throat now? Circle one.

0 No hurt · 1 Hurts a little bit · 2 Hurts a little more · 3 Hurts even more · 4 Hurts a whole lot · 5 Hurts worst

FUNCTION

2. Which of these faces shows how hard it is for your child to SWALLOW saliva/spit today because of mouth or throat pain? Circle one.

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't swallow · ☐ Can't tell

3. Which of these faces shows how hard it is for your child to EAT today because of mouth or throat pain? Circle on

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't eat · ☐ Can't tell

4. Which of these faces shows how hard it is for your child to DRINK today because of mouth or throat pain? Circle on

0 Not hard · 1 Little bit hard · 2 Little more hard · 3 Even harder · 4 Very hard · 5 Can't drink · ☐ Can't tell

PAIN MEDICATION

5. Has your child taken any medicine for any kind of pain today?
☐ Yes ☐ No

If yes, did your child need the medicine because of a sore mouth or throat?
☐ Yes ☐ No

APPEARANCE (The photos shown on the introduction page are examples of what mouth sores may look like).

6. Please look in your child's mouth. Can you see any mouth sores in your child's mouth today?
☐ Yes ☐ No ☐ Can't tell

From: Tomlinson D, Gibson F, Treister N, et al. Refinement of the Children's International Mucositis Evaluation Scale (ChIMES): child and parent perspectives on understandability, content validity and acceptability. *Eur J Oncol Nurs* 2010;14(1):29-41
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TABLE 2_SuppInfo Oral mucositis severity assessment tool utilized at Great Ormond Street Hospital (GOSH).

Oral Assessment Guide for Children and Young People

Category	Method of assessment	1	2	3
Swallow	Ask the child to swallow or observe the swallowing process. Ask the parent if there are any notable changes.	Normal. Without difficulty	Difficulty in swallowing	Unable to swallow at all Pooling, dribbling of secretions
Lips and corner of mouth	Observe appearance of tissue	Normal Smooth, pink and moist	Dry, cracked or swollen	Ulcerated or bleeding
Tongue	Observe the appearance of the tongue using a pen-torch to illuminate	Normal Firm without fissures (cracking or splitting) or prominent papilla Pink and moist	Coated or loss of papillae with a shiny appearance with or without redness and/or oral *Candida*	Ulcerated, sloughing or cracked
Saliva	Observe consistency and quality of saliva	Normal Thin and watery	Excess amount of saliva, drooling	Thick, ropy or absent
Mucous membrane	Observe the appearance of tissue using a pen-torch to illuminate the oral cavity	Normal Pink and moist	Reddened or coated without ulceration and/or oral *Candida*	Ulceration and sloughing with or without bleeding
Gingivae	Observe the appearance of tissue using a pen-torch to illuminate the oral cavity	Normal Pink or coral with a stippled (dotted) surface Gum margins tight and well defined, no swelling	Oedematous with or without redness, smooth	Spontaneous bleeding
Teeth (if no teeth score 1)	Observe the appearance of teeth using a pen-torch to illuminate the oral cavity	Normal Clean and no debris	Plaque or debris in localised areas	Plaque or debris generalised along gum line
Voice	Talk and listen to the child Ask the parent if there are any notable changes	Normal tone and quality when talking or crying	Deeper or raspy	Difficult to talk, cry or not talking at all

NB: if score >8 introduce pain assessment instrument

Oral assessment guide – Adapted from Eilers et al. (1988) by the mouth care working party at Great Ormond Street Hospital for Children NHS Trust (2005).

Accessed online April 2021:
https://media.gosh.nhs.uk/documents/Oral_Assessment_Guide_for_Children_and_Young_People_2.pdf
Adapted from:
Eilers J, Berger AM, Petersen MC. Development, testing, and application of the oral assessment guide. *Oncol Nurs Forum.* 1988;15(3):325-330.

Author, year	Analgesic agent, preparation	Bolus	Background	Lockout (mins)	Maximum dose, time period
Alonso Puig et al., 2020[41]	Morphine PCA 1mg/kg up to 50mg in 100ml (10mcg/kg/ml) *½ strength*	Bolus 1-2ml (10-20mcg/kg)	0-1ml/h (0-10mcg/kg/hr)	5	10ml/4hrs
Collins et al., 1996[43]	Morphine Hydromorphone	28mcg/kg 4mcg/kg Increase by 25-100% for incident pain	Start: 10 mcg/kg/hr Start: 1.4 mcg/kg/hr Increase by 25 – 100% if continuous pain	5	0.1 mg/kg 0.014 mg/kg 1 hour max
Dunbar et al., 1995[46]	Morphine 1 or 5mg/ml Hydromorphone 0.2 or 1mg/ml	20 mcg/kg 3 mcg/kg	In some: 40% opioid requirements last 24h. Night-time: 50% of previous night requirements.	8	NR
James et al., 2010[21] *	Up to 50 kg: morphine 1 mg/kg (± ketamine 1 or 2 mg/kg) in 50 ml	PCA: 0.5 or 1 ml (10 – 20 mcg/kg) NCA: 0.5 or 1 ml (10 - 20 mcg/kg)	PCA: 0 or 4mcg/kg/hr NCA: 0, 4, 10mcg/kg/hr Increase to 'out of protocol' based on individual needs	PCA: 5 NCA: 20	20 mls/ 4h (increase as needed)
	>50 kg = morphine 50 mg (± ketamine 50 mg or 100 mg) in 50ml	PCA: 1 ml (1mg) NCA: 1ml (img)	PCA: 0 or 0.2mg/hr NCA: 0, 0.2, 0.4mg/hr	PCA: 5 NCA: 20	20 mls/ 4h (increase as needed)
Mackie et al., 1991[49]	Morphine	PCA 15 mcg/kg	Night: average mg/h morphine required during the previous 16 h.	10	No limit
Oudot et al., 2011[50]	Morphine 1mg/ml Pethidine 5mg/ml	Loading 100-125mcg/kg bolus 15mcg/kg; If inadequate increase to 25, 35, then 40mcg/kg Pethidine: 5 times above	No background	15	8 bolus per 4hrs
Vasquenza et al., 2015[23]	Morphine Hydromorphone Fentanyl	20 mcg/kg 4 mcg/kg 0.5 mcg/kg	20 mcg/kg/hr 4 mcg/kg/hr 0.5 mcg/kg/hr	8-10	
White et al., 2011[22]	Morphine 1 mg/kg (± ketamine 1mg/kg) made up to 50 ml with 0.9% NS	PCA/NCA: 1–2 ml (20 – 40mcg/kg)	PCA/NCA: 0–2 ml/h (0–4 mcg/kg)	PCA: 5 NCA: 20	Morphine: 400 µg/kg (20mls in 4h); Morph + ket: 1000 µg/kg (50mls in 4h)

TABLE 3_SuppInfo PCA/NCA Programming reported by studies included in systematic review

* James et al, 2010 is previous study from Great Ormond Street Hospital, and utilises the same protocol as in the current case series.

TABLE 4_SuppInfo Correlation matrix of variables relating to episodes of IV opioid PCA/NCA for severe mucositis

	Duration (days)	Age (years)	Morphine Day 0	Morphine Day 1	Morphine Day 2
Duration n=359	1.0				
Age n=359	-.063	1.0			
	[-0.17, 0.04]				
Morphine D0 0; n=318	.16**	.15**	1.0		
	[0.04, 0.28]	[0.04, 0.26]			
Morphine D1; n=300	.34**	.07	.63**	1.0	
	[0.23, 0.44]	[-0.06, 0.19]	[0.53, 0.71]		
Morphine D2; n=276	.46**	.08	.46**	.79**	1.0
	[0.35, 0.57]	[-0.05, 0.19]	[0.36, 0.56]	[0.73, 0.84]	

Legend: Data represent two-tailed Spearman's rho [bias corrected 95%CI]; **correlation is significant at *p*=0.01 level