A Model for in situ Plan of Care for a Critically Unstable Pediatric Patient Following I-131 MIBG Infusion.

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Abbreviations key:

MIBG	metaiodobenzylguanidine
PICU	Pediatric Intensive Care Unit
mrem	milli-rem
mSV	milli-sievert
mCi	milli-Curie
kg	kilogram
yo	year old
RT	Respiratory Therapist
MD	Medical Doctor
RN	Registered Nurse
hr	hour
HemeOnc	Hematology/Oncology

Abstract:

Recent clinical trials have movedI-131 MIBG therapy into frontline management of high-risk neuroblastoma. With this expansion, it is reasonable to anticipate the need for intensive care level resuscitations. Radiation exposureremains the greatest risk to healthcare professionals managing these patients.We combined shock simulation scenario data with actualradiation dosimetry data to create a care model allowing for aggressive, prolonged *in situ* resuscitation of a critically ill pediatric patient after I-131 MIBG administration. This model will maintain a critical care provider's radiation level below10% of the annual occupational dose limit (5 mSv, 500mrem) per patient managed.

Introduction:

Radioactive MIBG (metaiodobenzylguanidine) therapy is a targeted radiotherapy agent historically used for the treatment of relapsed or refractory neuroblastoma. Based upon promising response rates, recent clinical trials are moving MIBG therapy into front-line management of high-risk neuroblastoma.[1-8]Radiation exposure from iodine-131 (I-131) remains the greatest risk to healthcare professionals managing these patients.[9-11] In the United States, occupational radiation dose limits are found in Title 10, Part 20 of the Code of Federal Regulations (10 CFR 20), or in equivalent Agreement State regulations. The annual adult occupational dose limitsare 50mSv (5,000 mrem), and 5 mSv (500 mrem) for the embryo/fetus of a declared pregnant woman(during the entire pregnancy).[11,12]

Due to Federal guidelines governing the release of individuals containing radioactive material (10 CFR 35.75),[13] patients receiving I-131 MIBG treatment are typically hospitalized in a shielded isolation room for 3-5 days, pending clearance of the I-

131.In the event of acute, critical decline, it is undesirable for these patients to travel to diagnostic imaging or surgical suite facilities, or to have radioactive diagnostic samples sent to a clinical laboratory. During the infusion and in the days that follow, trainedpediatric intensive care (PICU) and oncology team members are on-call to respond to emergencies including, but not limited to, sedation complications, anaphylaxis, septic shock, acute respiratory failure, cardiovascular instability (hypertensive crises, arrhythmias)and acute neurologic deterioration.

Radiation exposure tohealthcare professionals for routine care of patients receiving I-131 MIBG treatment are historically very low (<0.45 mSv = 45 mremper treatment).[14-16] Unfortunately, these data do not reflect a potentially protracted time period at the bedside that would be required to adequately resuscitate a pediatric patient after severe, acute deterioration. Because multiple MIBG therapy patients are managed at Michigan Medicine annually, as part of our clinical practice guideline, we have established a radiation exposure goal of 5 mSv (500 mrem), or 10% of the annual occupational dose limit per healthcare professional per patient managed. Our goal was to create a care model that would allow for aggressive, *in situ* resuscitation of a critically ill pediatric patient after I-131 MIBG administration, while controlling occupational radiation dosesfor all care providers, to remain within our radiation exposure limit.

Methods:

A failure mode effects analysisidentified staffing needs as our greatest barrier in resuscitating a patient with acute, severe shock immediately after MIBG infusion in the original acute care location. Therefore, we coupled dosimetry data from a

pediatric patient during and after MIBG infusion with data from a shock resuscitation simulation to generate a proposed staffing model.

Case Study: Concurrent with an existing MIBG treatment protocol approved by the Institutional Review Board, we placed fiveradiation dosimeters (Landauer OSL) in selected locations of the isolation room(Figure 1).An 11 yo female with high risk neuroblastoma received 811 mCi (15.1 mCi/kg) of I-131 MIBG.Dosimetersrecorded exposure over selected time intervals for the first 96 hours after the infusion started.

Shock scenario simulation: We also completed a paper simulation of a patient experiencing an acute shock-type event after the start of MIBG infusion and requiring 4 days of intensive care management*in situ*. The scenario chosen was cardiac arrest, requiring full resuscitative efforts, including placement of monitors, rapid sequence intubation, mechanical ventilation and suctioning, peripheral, central venous and arterial vascular access completed in series, initiation and titration of vasoactive infusions, administration of sedation, analgesia, antibiotics and other medications, and emergent diagnostic testing. Emergent diagnostic testing for the deteriorated MIBG patient was limited to point-of-care blood testing and chest and abdominal radiographs.

The shock simulation scenario data were merged with dosimetry datato estimate radiation doses for each team member, accrued across all time phases for the first 4days after MIBG administration. The scenario accounts for the dynamic movement of each team member amongfive different positionsin the isolation room (**Table1, Figure 1**)and radiation dose rate reduction from the physical decay[15] of Iodine-131 and biological clearance of MIBG. Assuming team members work 8- or 12-hour

shifts, we determined thestaffing modelrequired to effect this same care in a real-life situation(**Supplemental Table**).

Results:

The highest dose rate is in position 2,at bedside and in front of the lead shield. Estimates indicate that a team member can remain in position 2 for the first 5 hours after infusion, the time of greatest radiation exposure, before reaching 5mSv (500 mrem). The next highest dose rate is in position 1(head of the bed), although the dose rate was often less than 25% of the dose rate in position 2. Any position behind a lead shield results in substantially less exposure**(Table1, Figure 1).**

The simulation resulted in time-spent estimates of 288 minutes for PICU nurse, 155 minutes for PICU physician, 146 minutes for oncology nurse, 58 minutes for oncology physician, and 76 minutes for PICU Respiratory Therapist (RT).

Taken together, these data determined our staffing model**(Supplemental Table):**

a) *PICU physician*: Two pediatric intensivists will be necessary, each prepared to work 12-hour shifts for the first 96 hours afterthe start of MIBG infusion. A third intensivist should be available in the event that one of the two primary intensivists needs assistance.

b) *PICU nurse:* For the first 24 hours, six PICUnurses will be needed, each working 8-hour shifts and rotating in 4-hour intervals between positions 2 and 3. After the first 24 hours, PICU nurses may work a 12-hour shift in all positions.

c) *Respiratory therapist:* For all time periods, one RT will be needed and may work 12-hour shifts.

Discussion:

While maximal medical and surgical intensive care may not be an option for patients receiving MIBG therapy due to radiation safety concerns, this case study describes how critical care therapiesmaybe safely applied *in situ* for the first 4 days after the start of the infusion. Our data indicate that a team member spending all time at the location of highest radiation dose rate (at bedside and in front of the shield)would not exceed 10% of the annual occupational dose limit, unless remaining in that position for more than 5 hours. The goal of 5mSv (500mrem)per patientallows team members to safely manage multiple patients annually, even in the unlikely event of multiple deteriorations.

As these data reflect one patient and one simulation, our proposed model recommendsuse of real-time dosimeters for quick, on-demand monitoring, worn by each team member, with accumulated doses assessed after the first 4 hours and at 24-hour intervals to assist in refining the need for staffing rotation. When possible, we recommend only one physician, nurse, and respiratory therapist be in the room, and team members should stand near the

door or behind a lead shield. Finally, should any team member exceed 5 mSv (500 mrem,)we recommend they rotate out of the isolation room into the anteroom (position 5) for all remaining time.

As MIBG treatment trials expand enrollment to include younger children and infants, as well as intravenous or multi-drug sedatives to ensure patient tolerance of the treatment, it is reasonable to anticipate the need for intensive care level resuscitations.[17] Our model endorsesthat pediatric critical care level resuscitation and management can be achieved *in situ*while adequately controlling occupational radiation exposures.

Ongoing work is necessary to replicate our findings,perhaps with shorter monitoring periods, use of instantaneous monitoring, and in patients receiving different doses of I-131 MIBG.

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CONFLICTS OF INTEREST

The authors report no known conflicts of interest.

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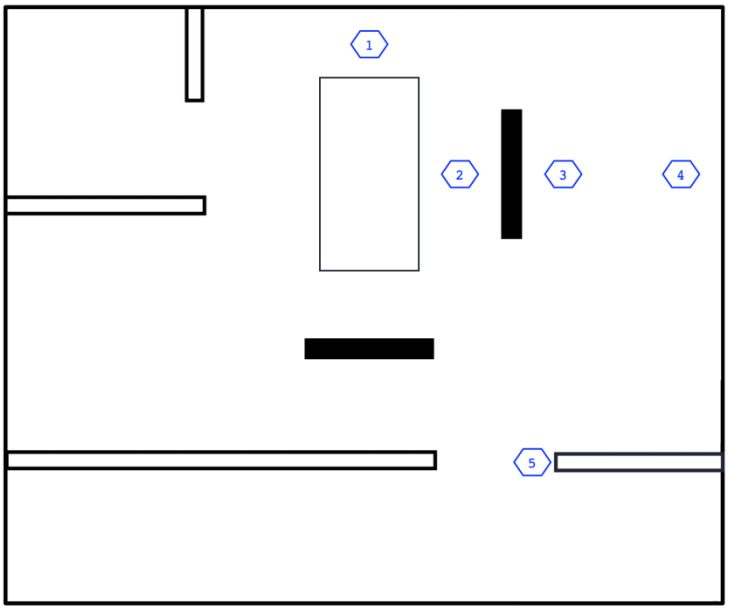

FIGURE 1 Schematic of actual patient room noting each of 5 radiation dosimeter locations.Dark lines represent portable lead shields. Double lines represent walls. Rectangle represents patient bed. Hexagons represent locations of dosimeters: 1 - at head of bed, 2 - at side of bed but in front of lead shield, 3 - at side of bed but behind lead shield, 4 – on wall within room, 5 – at doorway entrance to MIBG room

TABLE 1 Mean radiation doses (mrem/hr, 1mSv=100mrem)recorded over selected time intervals for the first 96 hours after I-131 MIBG infusion start at each of 5 patient room locations.(Note: *Exact time frame for this interval was 4 – 16.6 hrs.)

Time Period Dose Rate (mrem/hr)	0-4 hrs	4-16*hrs	16-24 hrs	24-48 hrs	48-75hrs	75-96 hrs
1 - Head of Bed	56	23	27	15	14	3
2 - Side of bed – in front of shield	103	89	96	59	34	21
3 - Side of bed – behind shield	5	2	1	<1	<1	<1
4 - Side wall of patient room	18	3	1	3	2	2
5 - Doorway to patient room	5	<1	<1	<1	<1	<1