# The Diagnosis and Management of a Perioperative Thyrotoxic Crisis

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#### **KEY POINTS**

- Thyroid storm is a life-threatening condition characterised by overt thyrotoxicosis in the setting of longstanding untreated or undertreated hyperthyroidism.
- It may be triggered by an acute stress event such as abrupt discontinuation of antithyroid medication, infection, or surgery.
- In the awake patient, neurological, cardiovascular, thermoregulatory, and gastrointestinal dysfunction characterise the predominant clinical abnormalities.
- In the anaesthetised patient, intraoperative signs may be limited to pyrexia, tachycardia, and atrial fibrillation, making the diagnosis more difficult.
- The differential diagnosis for an intraoperative thyroid storm should include sepsis, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, pheochromocytoma, and anticholinergic syndrome.
- Perioperative management should include general supportive measures (airway, breathing, circulation, and temperature management) as well as specific pharmacological interventions (beta-blockade, thionamide, iodine, and glucocorticosteroids).

## INTRODUCTION

A paucity of literature exists regarding the intraoperative recognition and management of a thyrotoxic crisis, more commonly known as a thyroid storm. Due to the rarity of this condition<sup>1-3</sup> and the various nonspecific clinical manifestations of a thyroid storm under anaesthesia,<sup>4</sup> prompt diagnosis and initiation of treatment remain a challenge but are very important.<sup>5</sup> This tutorial will focus on this rare but life-threatening complication of thyrotoxicosis, provide a stepwise approach to supportive and pharmacological management, and provide guidance on the optimisation of patients in the perioperative period.

## Definition

Hyperthyroidism, thyrotoxicosis, and thyroid storm are 3 separate clinical conditions that should not be confused with one another.

• Hyperthyroidism is a biochemical diagnosis that is defined by an increase in circulating thyroid hormone levels.<sup>6</sup>

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- Thyrotoxicosis refers to a group of signs and symptoms induced by the thyroid hormones' inappropriate activation in the tissue and should be seen as the clinical manifestation of hyperthyroidism.<sup>6</sup>
- A thyroid storm is an acute life-threatening endocrine emergency resembling an exaggerated presentation of thyrotoxicosis.<sup>7</sup>

# **Basic Thyroid Physiology**

The thyroid's main function is to convert iodine into thyroid hormones: the prohormone thyroxine (T4) and the bioactive hormone triiodothyronine (T3). Thyroid cells combine iodine and tyrosine to form T3 and T4. The normal thyroid gland produces about 80% T4 and 20% T3. The majority of T3 is produced by enzymatic deiodination of T4 in peripheral tissues by iodothyronine deiodinases. The thyroid gland is under the control of the anterior pituitary gland, which secretes thyroid-stimulating hormone (TSH) and stimulates the production of T3 and T4. TSH is produced and released from the anterior pituitary gland in response to thyrotropin-releasing hormone (TRH) released from the hypothalamus and carried to the pituitary via the hypothalamohypophyseal portal system. The hypothalamus can also inhibit TSH secretion via the effects of released somatostatin, in the same way that growth hormone inhibition occurs. Free T3 and free T4 in the plasma exert a negative feedback effect on the hypothalamus and the pituitary to regulate the circulating levels.<sup>8</sup>

#### **Incidence and Mortality**

The majority of epidemiological data on thyroid storm are from national surveys in Japan and the United States. Thyroid storm incidence ranges from 0.20 to 0.76 per 100 000 people per year.<sup>9,10</sup> Intraoperative and postoperative thyroid storm following nonthyroid surgery has rarely been reported, with 24 cases identified in the literature between 1930 and 2018.<sup>5</sup> The rarity of this intraoperative emergency is due to the widespread use of antithyroid medication to achieve a euthyroid state prior to surgery. Mortality rates of thyroid storm range between 10% and 30% despite early diagnosis.<sup>1,7,9</sup>

## **Clinical Features**

Symptoms of thyrotoxicosis include heat intolerance, palpitations, anxiety, fatigue, weight loss, muscle weakness, and, in women, irregular menses. Clinical findings may include tremors, tachycardia, lid lag, and warm moist skin. The clinical picture of thyroid storm is characterised Cby nonspecific signs ranging from thermoregulatory dysfunction to thyrotoxic heart disease (cardiothyreosis)<sup>1</sup> (Table 1).

# **CLINICAL MANIFESTATION**

The exact mechanisms underlying the development of a thyroid storm are poorly understood. Thyroid storm occurs in undiagnosed or uncontrolled hyperthyroidism or thyrotoxicosis in the presence of a trigger.<sup>11</sup> A heightened cellular response to thyroid hormone is implicated, as seen during acute stress. The increased or abrupt availability of free hormones results in enhanced responsiveness to catecholamines. It is postulated that a rapid increase in thyroid hormone, rather than the actual hormone level, leads to the development of a thyroid storm. A thyroid storm must be triggered regardless of the aetiology of hyperthyroidism and thyrotoxicosis; however, in up to 30% of patients no trigger can be identified.

# Triggers

Thyroid storm can develop in untreated or poorly controlled hyperthyroidism but it is more commonly precipitated by an acute event. The literature describes several precipitating factors, or triggers, including abrupt discontinuation of antithyroid medication, infection, surgery (thyroid and nonthyroid), trauma, preeclampsia, parturition, hyperemesis gravidarum, diabetic ketoacidosis, and acute iodine overload (radioactive iodine treatment, iodine in contrast studies, and oral iodine) (Table 2).<sup>2,3</sup>

Organ System	The Awake Patient	The Anaesthetised Patient
Central nervous system	Confusion, agitation, delirium, psychosis, seizure, stupor, coma	Seizure, delayed emergence
Cardiovascular system	Sinus tachycardia, hypotension, dysrhythmias (espe cardiac failure	cially atrial fibrillation), congestive
Thermoregulation	Pyrexia, dehydration	
Gastrointestinal system	Nausea, vomiting, abdominal pain, diarrhoea, hepatocellular dysfunction (jaundice)	Hepatocellular dysfunction (jaundice)

 Table 1. Clinical Features of Perioperative Thyroid Storm

General Triggers
Nonthyroid surgery
Trauma
Infection
Pulmonary embolism
Myocardial infarction
Diabetic ketoacidosis
Pregnancy related:
Preeclampsia
Parturition
Hyperemesis gravidarum
Thyroid-Related Triggers
Thyroid surgery
Abrupt discontinuation of antithyroid medication
Overdose of thyroid hormone
Acute iodine load:
Radioactive iodine treatment
Contrast dye
Oral iodine

Table 2. Thyroid Storm Triggers

# Diagnosis

The diagnosis of thyroid storm is challenging due to the nonspecific clinical features and rarity. The diagnosis is further hampered due to the continuum of severity ranging from thyrotoxicosis to thyroid storm. No laboratory abnormalities are specific to thyroid storm. Hyperthermia, mental state changes (irritability, delirium, psychosis, lethargy, coma), hypotension, tachycardia, dysrhythmias, and gastrointestinal and hepatocellular dysfunction characterise the clinical scenario in an awake patient with thyroid storm (Table 1).<sup>9</sup>

The diagnosis of intraoperative storm is a difficult task as the only clues may be intraoperative pyrexia and tachycardia. Mental state changes and gastrointestinal dysfunction will not be detected in a patient under general anaesthesia. Tachycardia has numerous causes and may indicate pain, awareness, hypovolemia, haemorrhage, medication side effects, or bladder distension. A rise in temperature and end-tidal carbon dioxide may be a sign of sepsis, malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome, pheochromocytoma, or anticholinergic syndrome.<sup>12</sup> Atypical presentations have been described under general anaesthesia in which the patient does not develop a fever. In the setting of a caesarean section under neuraxial anaesthesia, haemorrhage and hormonal changes can obscure the symptoms of thyrotoxicosis, making the intraoperative diagnosis even more challenging.

A stepwise diagnostic approach should be followed when a patient under general anaesthesia develops intraoperative tachycardia or pyrexia (Figure).<sup>13,14</sup> The differential diagnosis for pyrexia and tachycardia should be considered initially (Table 3).<sup>12</sup>

# **Diagnostic Tools**

Certain diagnostic tools can aid in diagnosing a thyroid storm in the awake patient in the preoperative and postoperative periods. The Burch and Wartofsky point scale (BWPS) described in 1993 uses nonspecific features to predict the likelihood of a thyroid storm (Table 4).<sup>3</sup> The BWPS has been widely applied for the diagnosis of thyroid storm for more than 2 decades. Central nervous system disturbances are heavily weighted in the BWPS; however, in the anaesthetised patient these disturbances will not be detected. In 2012, the Japanese Thyroid Association proposed diagnostic criteria (the Akamizu diagnostic criteria) that include thyrotoxicosis as a prerequisite condition (Table 5).<sup>13</sup> Using both scores to evaluate an awake patient's condition is recommended to increase diagnostic accuracy. These diagnostic criteria are helpful because they provide a systematic framework to think about the diagnosis. However, we are not forced to rigidly adhere to these criteria for 2 reasons. Firstly, the diagnosis of thyroid storm is partially a diagnosis of exclusion. For example, sepsis with multi-organ failure could easily score > 45 on the BWPS. Therefore, a score > 45 does not prove a diagnosis of thyroid storm. Secondly, treatment for thyroid storm is reasonable in any patient with severe hyperthyroidism causing organ failure (especially heart failure). Therefore, even if the patient does not have a score > 45 on the BWPS, it may be prudent to initiate therapy for thyroid storm.

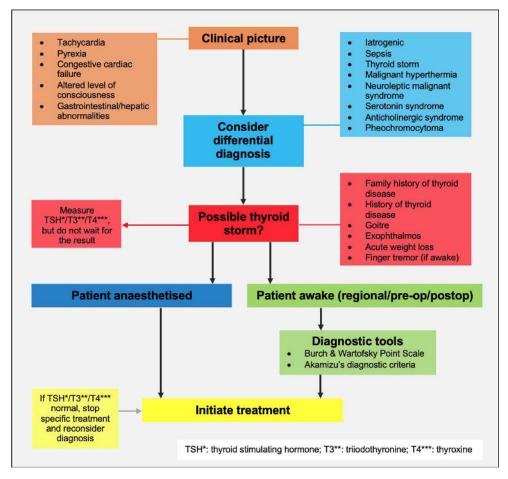


Figure. Diagnostic algorithm in perioperative thyroid storm.

# MANAGEMENT OF INTRAOPERATIVE THYROID STORM

Once the preliminary diagnosis of a thyroid storm has been made, prompt initiation of treatment is of utmost importance. The treatment options for thyroid storm are expanded from those used for uncomplicated hyperthyroidism. The principles of

Diagnosis	Exposure	Mental Status in Awake Patient	Pupils (If No Opioids Are Given)	Muscle Tone in Unparalyzed Patient	Mucosa and Skin	Reflexes in Awake Patient
Sepsis	Infection	Potentially impaired	Normal	Normal	Wet or Dry	Normal
Thyroid storm	Trigger	Potentially impaired	Normal	Normal	Normal	Normal
Malignant hyperthermia	Volatiles, succinylcholine	Impaired	Normal	Rigid	Wet	Decreased
Neuroleptic malignant syndrome	Antipsychotics	Impaired	Normal	Rigid	Wet	Decreased
Serotonin syndrome	Serotonergics (antidepressants, fentanyl, tramadol, linezolid, sumatriptan, ondansetron)	Impaired	Dilated	Rigid	Wet	Increased
Anticholinergic syndrome	Anticholinergics	Impaired	Dilated	Normal	Dry	Normal
Pheochromocytoma	Trigger	Normal	Dilated	Normal	Normal	Normal
latrogenic	Forced air warmer, increased ambient temperature	Normal	Normal	Normal	Normal/Dry	Normal

Table 3. Differential Diagnosis for Intraoperative Pyrexia and Tachycardia

Criteria	Points
(1) Thermoregulatory dysfunction	
Temperature (°C)	
37.2-37.7	5
37.8-38.3	10
38.4-38.8	15
38.9-39.3	20
39.4-39.9	25
> 40.0	30
(2) Cardiovascular	
Tachycardia (beats/min)	
90-109	5
110-119	10
120-129	15
130-139	20
> 140	25
Atrial fibrillation	
Absent	0
Present	10
Congestive heart failure	
Absent	0
Mild	5
Moderate	10
Severe	15
(3) Gastrointestinal-hepatic dysfunction	
Absent	0
Moderate (diarrhoea, abdominal pain, nausea/vomiting)	10
Severe (jaundice)	20
(4) Central nervous system disturbance	
Absent	0
Mild (agitation)	10
Moderate (delirium, psychosis, extreme lethargy)	20
Severe (seizure, coma)	30
(5) Precipitating event	
Absent	0
Present	10
Total score	
> 45: Thyroid storm	
25-44: Impending storm	
< 25: Storm unlikely	

Table 4. The Burch and Wartofsky Point Scale

treatment outlined below are based on clinical experience, case studies, the 2016 Japan Thyroid Association Guideline,<sup>13</sup> and the 2016 American Thyroid Association Guideline.<sup>14</sup>

Management principles can be divided into general considerations and specific considerations (Table 6),<sup>13,14</sup> and encompass the following:

- (1) Consideration and exclusion of the differential diagnoses,<sup>12</sup>
- (2) If thyroid storm is likely, implementation of the "ABCs of the Convulsing Hot Hormonal heart" (Table 6), and
- (3) Consideration of thyroidectomy in refractory cases and plasma exchange in thyroid storm complicated with acute hepatic failure.<sup>13</sup>

## **OPTIMISATION PRIOR TO SURGERY**

If hyperthyroidism or thyrotoxicosis is diagnosed in the preoperative period in a patient scheduled for elective surgery, it is recommended that surgery and anaesthesia be postponed until the patient is clinically and biochemically euthyroid. Achieving a euthyroid state can take anything from 6 weeks up to 18 months. In consultation with an endocrinologist the patient should be

Prerequisites		
Thyrotoxicosis with	elevated levels of free triiodothyrol	nine (FT3) or free thyroxine (FT4)
Manifestation		Symptom
CNS Fever Tachycardia CHF Gastrointestinal (GI)	Temperature > 38 Heart rate > 130 Pulmonary oedem Class IV by the	irium, psychosis, lethargy, coma 3°C beats/min or heart rate > 130 beats/min in atrial fibrillation ha, rales over more than half of the lung field, cardiogenic shock, or New York Heart Association <sup>13</sup> or > Class III in the Killip classification <sup>13</sup> diarrhoea, or a total bilirubin > 3.0 mg/dL
Grade of Thyroid Storm	Combination of Features	Requirements for Diagnosis
1	First combination Alternate combination	Thyrotoxicosis and at least one CNS manifestation and fever, tachycardia, CHF, or GI or hepatic manifestations Thyrotoxicosis and at least 3 combinations of fever, tachycardia,
2	First combination	CHF, or GI or hepatic manifestations Thyrotoxicosis and a combination of 2 of the following: fever, tachycardia, CHF, or GI or hepatic manifestations
2	Alternate combination	Patients who met the diagnosis of thyroid storm Grade 1 except that serum FT3 or FT4 level are not available

**Table 5.** Akamizu Diagnostic Criteria: Symptoms. Grade 1 indicates a definite thyroid storm and Grade 2 a suspected thyroid storm. Cases are excluded if other underlying diseases clearly cause any of the following symptoms: fever (eg pneumonia and malignant hyperthermia), impaired consciousness (eg psychiatric disorders and cerebrovascular disease), heart failure (eg acute myocardial infarction), and liver disorders (eg viral hepatitis and acute liver failure). Therefore, it is difficult to determine whether the symptom is caused by a thyroid storm or is simply a manifestation of an underlying disease; the symptom should be regarded as being due to a thyroid storm that is caused by these precipitating factors. Clinical judgement in this matter is required. CNS indicates central nervous system; CHF, congestive heart failure; FT3, free triiodothyronine; FT4, free thyroxine; GI, gastrointestinal

followed up initially after 4 to 6 weeks, then at month 3, month 6, and then at yearly intervals. In the setting of emergency surgery where optimisation might not be an option, a perioperative thyroid storm should be anticipated and adequately prepared for. Premedication in the form of a beta-blocker (propranolol 0.1-0.15 mg/kg intravenously [IV]), antithyroid drug (propylthiouracil 200-400 mg orally), and a corticosteroid (hydrocortisone 300 mg IV) should be administered. Where possible, regional anaesthesia and peripheral nerve block are preferable to general anaesthesia. If the surgical procedure does not allow for a regional anaesthetic technique, proceed with general anaesthesia ensuring that the intubation response is blunted, analgesia and depth of anaesthesia are adequate, and a smooth emergence and extubation are performed.<sup>15</sup> Vigilance regarding thyroid storm should extend into the postoperative care period; therefore it is recommended that the patient be monitored in a high-dependency unit.

## SUMMARY

Thyroid storm in an awake patient remains an elusive diagnosis. In an anaesthetised patient, the diagnosis is even more challenging, and the pharmacological treatment options are limited to a few intravenous medications. In the awake patient, the BWPS and the Akamizu's diagnostic criteria should form part of the anaesthetist's assessment. When tachycardia and pyrexia are noted in the patient receiving general anaesthesia, the differential diagnosis including thyroid storm should be considered.

And the waters leapt, And the wild winds swept, And blew out the moon in the sky, And I laughed with glee, It was joy to me As the storm went raging by! The rising of the storm, by Paul Laurence Dunbar

			ABCs	
General Considerations	<ul> <li>Inform the surgeon, de</li> <li>Protect the airway in a</li> <li>Increase FiO<sub>2</sub> and opt and establish second</li> <li>Consider differential d</li> <li>Treat the trigger, e.g.</li> <li>Refractory disease: co</li> <li>Thyroid storm complice</li> </ul>	in awake patient and imise ventilation if in intravenous access iagnosis (Table 3) manage infection (T onsider thyroidectom ated with acute hep	d administer suppler itubated, confirm fur able 2) iy atic failure: consider	nctioning intravenous acces
			ing" - Seizures	
	Treatment goal	Drug	Dose	Notes
		Lorazepam	0.1mg/kg IV (max:4mg)	*May repeat IV dose once
	Terminate convulsion	Diazepam	0.15-0.2mg/kg IV (max:10mg) or 0.2-0.5mg/kg PR (max:20mg)	*May repeat IV dose once *PR alternative if no peripheral IV access available
		Midazolam	0.2mg/kg buccal/ intra- nasal (max: 10mg) or 10mg IM (>40kg) or 5mg IM (13- 40kg)	*Buccal, intranasal, and intramuscular alternatives no peripheral IV access available
		Phenytoin	18mg/kg IV	*Maximum administration rate 50mg/minute
		Propofol	1-2mg/kg IV	*Administer if convulsions continue
	Treatment goal	Drug	" - Pyrexia Dose	Notes
Specific Considerations	Active mechanical cooling & pharmacological management	Paracetamol	1g IV/oral/NG or 500mg PR	*Non-steroidal anti- inflammatory agents not recommended because they increase free thyroid hormone levels *Cooling: icepacks in axillae and cooling blanke
		"Hormonal" - t	he Thyroid Hormo	
	Treatment goal	Drug	Dose	Notes
	Block synthesis of new thyroid	Propylthiouracil (PTU)	500-1000mg oral/NG/PR loading dose, then 200-250mg q4h	*American Thyroid Association guideline *Caution: liver toxicity *IV preparation not available
	hormones - Thionamides	Methimazole (MMI)	60mg oral/NG/PR or 30mg/day IV	*Japan Thyroid Associatio guideline
		Carbimazole (CBZ)	20mg q4-6h oral/NG/PR	*Avoid in pregnancy
	Block the release of preformed thyroid hormones	Lugol's solution (Potassium iodide-iodine solution)	5-10 drops oral/NG/PR	*Administer at least 1 hou after thionamide
		SSKI (saturated solution of potassium iodide)	5 drops oral/NG/PR	*No IV preparation
		lopanoic Acid (lodinated radiocontrast	1000mg IV q8h for 24h, then 500mg IV bd	*Administer at least 1 hou after thionamide *Infrequently available

 Table 6. Management Principles: The "ABCs of the Convulsing Hot Hormonal Heart"

		Esmolol	1 mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 1-2mg/min	*Japan Thyroid Association guideline *Titrated to heart rate < 130 bpm *Contraindicated in acute decompensated heart failure with systolic dysfunction *Titrated to heart rate <
	Block increased adrenergic tone	Propranolol	q15min up to max 10mg or 40-80mg PO/NG q4-6h	130 bpm *Contraindicated in acute decompensated heart failure with systolic dysfunction
		Metoprolol Diltiazem	100mg PO/NG q6h	*Cardioselective; use if known hyperreactive airway disease *Use if beta-blocker
		Diitiazem	60-90mg PO/NG q6-8h	contraindicated
		Propranolol	1-2mg/min q15min up to max 10mg or 40-80mg PO/NG q4-6h	*Titrated to heart rate < 130 bpm *Contraindicated in acute decompensated heart failure with systolic dysfunction
	Block peripheral T4 to T3 conversion	Hydrocortisone	300mg IV loading dose, then 100mg IV q8h	
		Dexamethasone	8mg IV daily	
Specific		lopanoic Acid	1000mg IV q8h	*Administer at least 1 hour
Considerations		(lodinated radiocontrast	for 24h, then 500mg IV bd	after thionamide *Infrequently available
		agent)		
			accular Manifactat	ions
	Treatment goal	"Heart" - Cardiov	ascular Manifestat Dose	
	Treatment goal Manage Tachycardia		ascular Manifestat Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate	Notes *Japan Thyroid Association guideline *Titrated to heart rate < 130 bpm *Contraindicated in acute decompensated heart failure with systolic dysfunction
	Manage	"Heart" - Cardiov Drug Esmolol Digoxin	Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 8-12mcg/kg IV (total loading dose in divided increments: 50% initially, then 25% after 6h, then 25% after 6h)	Notes *Japan Thyroid Association guideline *Titrated to heart rate < 130 bpm *Contraindicated in acute decompensated heart failure with systolic dysfunction *Digoxin IV recommended in the absence of severe renal dysfunction
	Manage Tachycardia Manage Atrial	"Heart" - Cardiov Drug Esmolol Digoxin Amiodarone	Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 8-12mcg/kg IV (total loading dose in divided increments: 50% initially, then 25% after 6h, then 25% after 6h) 150mg IV over 10 minutes, then 1mg/min IV for 6h, then 0.5mg/min IV	*Japan Thyroid Association guideline         *Titrated to heart rate <
	Manage Tachycardia Manage Atrial fibrillation	"Heart" - Cardiov Drug Esmolol Digoxin Amiodarone Furosemide	Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 8-12mcg/kg IV (total loading dose in divided increments: 50% initially, then 25% after 6h, then 25% after 6h) 150mg IV over 10 minutes, then 1mg/min IV for 6h, then 0.5mg/min IV 0.5-1mg/kg IV over 1-2 minutes	*Japan Thyroid Association guideline         *Titrated to heart rate <
	Manage Tachycardia Manage Atrial fibrillation	"Heart" - Cardiov Drug Esmolol Digoxin Amiodarone	Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 8-12mcg/kg IV (total loading dose in divided increments: 50% initially, then 25% after 6h, then 25% after 6h) 150mg IV over 10 minutes, then 1mg/min IV for 6h, then 0.5mg/min IV 0.5-1mg/kg IV over 1-2 minutes 2.5-10 ug/kg/min IV	*Japan Thyroid Association guideline         *Titrated to heart rate <
	Manage Tachycardia Manage Atrial fibrillation	"Heart" - Cardiov Drug Esmolol Digoxin Amiodarone Furosemide	Dose 1mg/kg IV over 30 seconds, then 150 mcg/kg/min titrated to heart rate 8-12mcg/kg IV (total loading dose in divided increments: 50% initially, then 25% after 6h, then 25% after 6h) 150mg IV over 10 minutes, then 1mg/min IV for 6h, then 0.5mg/min IV 0.5-1mg/kg IV over 1-2 minutes 2.5-10	*Japan Thyroid Association guideline         *Titrated to heart rate <

Table 6. Continued.

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