Sinusoidal Obstruction Syndrome / Veno-Occlusive Disease

The ANZTCT practice statement

Diagnosis, prevention and management in Australasian HSCT practice

Fleming S, et al. on behalf of the ANZTCT | Intern Med J 2024;54:1548–1556

Why an Australasian practice statement?

Heterogeneous disease

Biologically and clinically variable, with competing diagnostic criteria in concurrent use

Variable access

TGA: severe disease only. Pharmac: moderate and severe. Adult access more restricted than paediatric

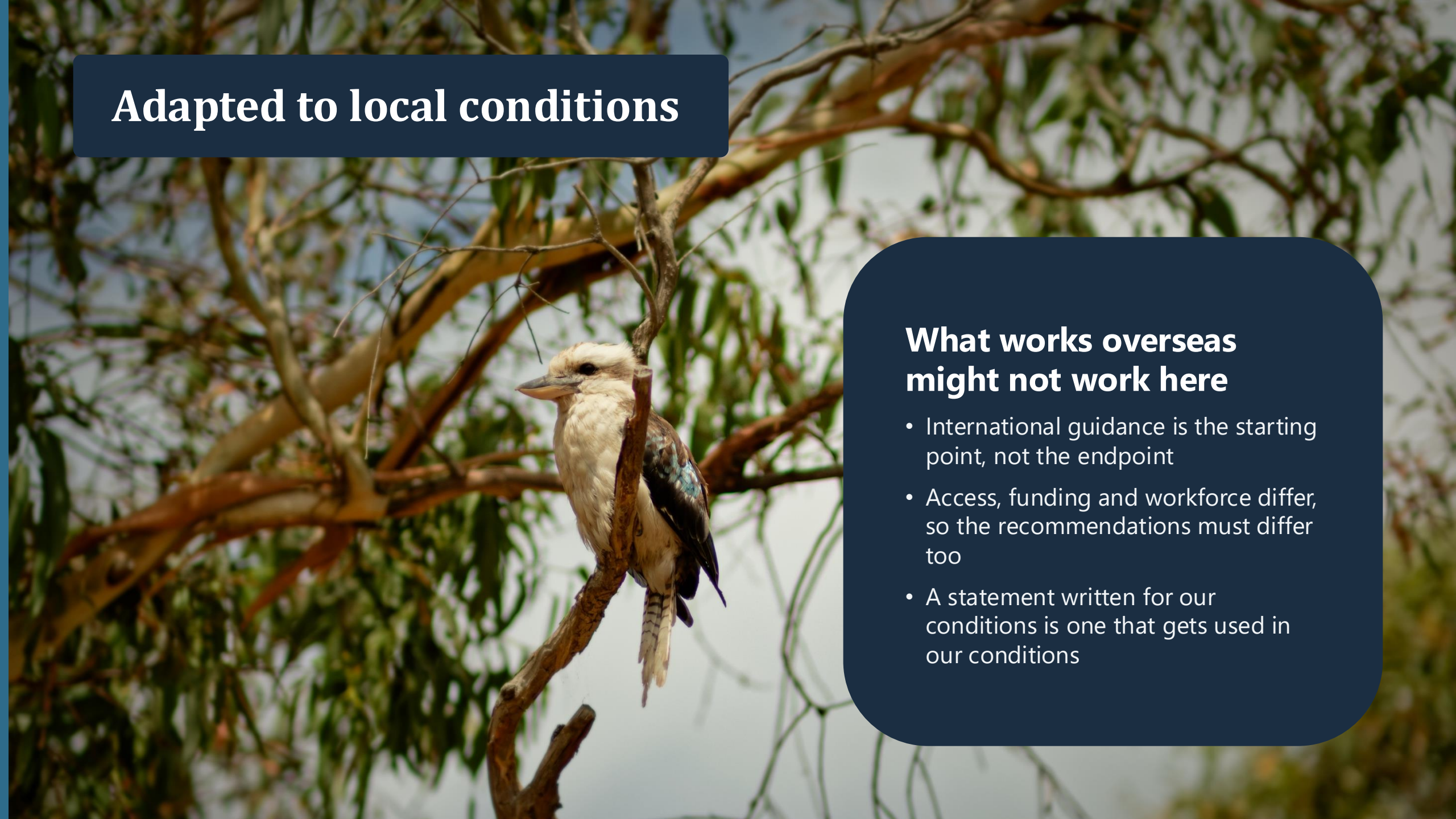
Variable practice

Defibrotide dose and duration differ significantly across adult centres

A single Australasian reference point

Consensus recommendations for diagnosis, prevention and treatment

Adapted to local conditions



What works overseas might not work here

- International guidance is the starting point, not the endpoint
- Access, funding and workforce differ, so the recommendations must differ too
- A statement written for our conditions is one that gets used in our conditions

Pathophysiology: a cascade, not an event

Endothelial insult

Chemotherapy, TBI, busulfan, cytokines and ADCs injure zone 3 sinusoidal endothelium

Sloughing

Damaged endothelial lining detaches and embolises downstream

Obstruction

Progressive venular narrowing, then complete venular destruction

Hepatic necrosis

Extensive necrosis of surrounding hepatocytes

Reduced hepatic outflow

Non-cirrhotic portal hypertension, fluid overload, ascites, painful hepatomegaly

Synthetic dysfunction

Hyperbilirubinaemia and coagulopathy

Unless arrested: fulminant hepatic failure and/or multiorgan failure

80% mortality once multiorgan failure develops

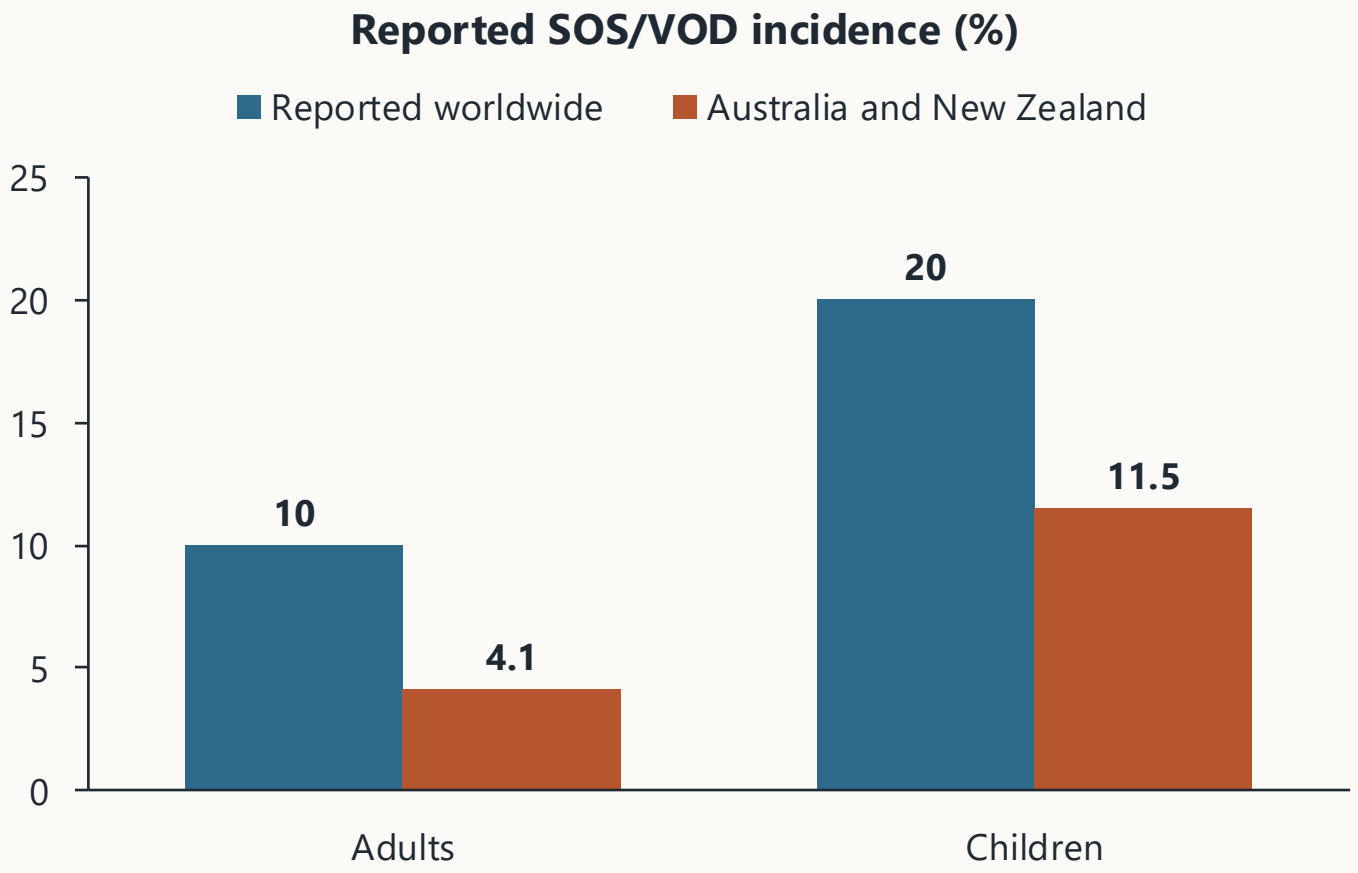
Timing: classical versus late onset

Classical	Late onset
Day 0 to day 21	Beyond day 21 after HSCT
Bilirubin of 2 mg/dL or more is required for a clinical diagnosis in this window	Bilirubin is less consistent late; EBMT 2023 places no limitation on time of onset

Why the time limit matters

Anchoring diagnosis to the first 21 days and to a fixed bilirubin threshold misses disease that is already established. Removing both is what allows late-onset SOS/VOD to be captured.

How common, and how lethal



80%

Mortality once multiorgan failure develops

23%

Of proven cases have bilirubin below 2 mg/dL at diagnosis

Risk: what you can change, and what you cannot

	Transplant	Patient and disease	Hepatic
Cannot be modified	Unrelated donor selection	Age, disease status, genetic predisposition (GSTM1, MTHFR, C282Y)	Established cirrhosis
Can be modified	Myeloablative conditioning, particularly TBI or busulfan; PK-guided busulfan dosing	Timing of HSCT relative to prior therapy; delay until major risk factors addressed	Baseline liver function, active hepatitis, concurrent hepatotoxins including azoles, prior GO or InO

Antibody–drug conjugates change the risk calculus

Inotuzumab ozogamicin

INO-VATE: 14.0% versus 2.1% with standard-of-care chemotherapy

19% after allogeneic HSCT in patients previously given InO

6.6-fold higher incidence with two alkylating agents versus one

Gemtuzumab ozogamicin

15–40% when HSCT is performed within 3 months of GO

Odds ratio 21.6 for SOS/VOD with prior GO exposure

Fractionated, lower dosing (median 3 mg/m^2) may mitigate risk

Recommended washout: InO

Maximum two cycles (six doses), then at least 6 weeks before starting HSCT

Recommended washout: GO

At least 12 weeks after the last dose before starting HSCT

Diagnosis

Three competing criteria — and why the choice changes who gets treated

Three sets of criteria, three different answers

Modified Seattle	Baltimore	EBMT 2023
Hyperbilirubinaemia is mandatory	Hyperbilirubinaemia is mandatory	No limitation on time of onset
Time-limited to the early window after HSCT	Time-limited to the early window after HSCT	Bilirubin not mandatory for a probable diagnosis
Criticised for relatively poor capacity to diagnose early	Same limitation: diagnosis often comes late	Probable, clinical and proven categories
		Severity graded, with multiorgan dysfunction defined by SOFA

Late diagnosis means late treatment, and outcomes in severe disease are poor

EBMT 2023 in adults: probable, clinical, proven

Any two of the following

- Bilirubin 2 mg/dL or more (34 µmol/L)
- Painful hepatomegaly
- Weight gain above 5%
- Ascites
- Ultrasound or elastography suggestive of SOS/VOD

No limitation on time of onset

Probable

Two or more criteria met. Bilirubin is not required.

Clinical

Same criteria, but bilirubin must be 2 mg/dL or more.

Proven

Histology, or HVPG of 10 mmHg or more.

Severity grading in adults

Mild	Bilirubin 2 to under 3 · transaminases up to 2× normal · creatinine at baseline · onset more than 7 days ago
Moderate	Bilirubin 3 to under 5 · transaminases over 2 to 5× · creatinine under 1.5× baseline · onset 5 to 7 days ago
Severe	Bilirubin 5 to under 8 · transaminases over 5 to 8× · creatinine 1.5 to under 2× baseline · onset within 4 days
Very severe	Bilirubin 8 or more · transaminases over 8× · creatinine 2× baseline or multiorgan dysfunction · any time

Bilirubin in mg/dL (2 mg/dL = 34 µmol/L). Doubling within 48 hours, or two or more mild-to-moderate risk factors, moves the patient up a grade. Multiorgan dysfunction is always very severe.

Imaging, confirmation and the differential

1. It remains a clinical diagnosis

Criteria are applied at the bedside; nothing else is required to start treatment

2. Imaging is an adjunct only

Ultrasound, Doppler, contrast-enhanced ultrasound, CT, MRI and elastography are all described but uncommonly used. Most valuable read against pre-HSCT baseline imaging.

3. Confirmation is rarely pursued

HVPG of 10 mmHg or more, with transjugular biopsy, is the gold standard. Procedural bleeding risk means it is seldom performed.

Think about, or alongside

- Hepatic graft-versus-host disease
- Thrombotic microangiopathy
- Drug hepatotoxicity and sepsis

These processes can occur concurrently with SOS/VOD. Where they do, both need treating.

Prevention and treatment

Prevention is still the most effective strategy we have

The prevention pathway

Assess

- Prospective risk assessment for every HSCT recipient
- Stipulate a minimum acceptable level of liver function

Modify

- Non-TBI or reduced-intensity conditioning
- Avoid dual alkylators
- PK-guided busulfan dosing
- Avoid hepatotoxins, monitor azoles

Wash out

- InO: two cycles maximum, then 6 weeks or more
- GO: 12 weeks before HSCT

Prophylax

- Ursodeoxycholic acid from the start of conditioning to day +90
- Heparin is not recommended

Where possible, delay HSCT until major risk factors have been addressed

Prevention remains the most effective strategy available

What the prophylaxis evidence actually shows

Ursodeoxycholic acid
Recommended

- Systematic review of three randomised studies: relative risk 0.34 (95% CI 0.17 to 0.66)
- Randomised study of 242 patients at 10 years: overall survival 48% versus 38% (p = 0.037)
- Non-relapse mortality 28% versus 41% (p = 0.01)
- Give from the start of conditioning to day +90

Heparin
Not recommended

- Rationale was clot prevention; disease biology does not support it
- Multiple analyses show no conclusive benefit
- Bleeding risk in thrombocytopenic HSCT patients

Defibrotide
Unresolved

- HARMONY (n = 372): SOS/VOD-free survival at day 30 of 67% versus 73% (p = 0.85)
- Powered on an assumed 28% control incidence, so likely underpowered
- Endpoint ignored morbidity; controls could receive defibrotide on diagnosis
- Paediatric Prevention trial: 20% reduced to 12% (p = 0.049)

Managing established disease

Supportive care is the backbone

Arguably more important than any specific agent

- Aggressive optimisation of volume status: diuretics, salt and water restriction, dialysis
- Drainage of ascites and pleural effusions
- Analgesia
- Avoidance of hepatotoxins and nephrotoxins
- Respiratory support

Defibrotide

25 mg/kg/day, at least 14 to 21 days, continued until all symptoms resolve, then weaned after response

Phase III, 102 patients with severe disease: day +100 survival 38.2% versus 25% ($p = 0.0109$); complete response 25.5% versus 12.5% ($p = 0.0160$)

Escalate early

Involve a specialist hepatology unit early in severe disease, and consider a transjugular intrahepatic portosystemic shunt

The access gap: who can be treated, and when

	Mild	Moderate	Severe	Very severe
EBMT recommendation	*Not included*	From moderate disease onwards		
New Zealand: Pharmac	*Not included*	Funded for moderate and severe disease		
Australia: TGA	*Not approved*		Approved for severe hepatic SOS/VOD only	

Australian adults who received defibrotide had significantly worse overall survival, because it was reserved for the most advanced disease

Dose and duration are consistent across paediatric centres but vary significantly between adult centres (dose p = 0.04, duration p = 0.035). Earlier treatment improves survival and reduces cost.

Paediatric SOS/VOD

Apologies – coming from a non-paediatrician

Children present differently

Why children differ

- Incidence roughly double that of adults: 20% versus 10% worldwide, 11.5% versus 4.1% in ANZ
- Anicteric disease is more common
- Up to 20% present beyond day 30
- Higher-risk conditions: haemophagocytic lymphohistiocytosis, transfusion-dependent anaemia with iron overload and hepatic fibrosis, osteopetrosis
- Thrombotic microangiopathy and GVHD sit in the differential and may co-exist

EBMT paediatric criteria

No limitation on time of onset. No predefined bilirubin threshold.

- Unexplained consumptive, transfusion-refractory thrombocytopenia: often the first sign and a highly sensitive early marker
- Unexplained weight gain on three consecutive days despite diuretics, or more than 5% above baseline
- Rising bilirubin from baseline on three consecutive days, or 2 mg/dL or more within 72 hours
- Hepatomegaly above baseline, best confirmed on imaging
- Ascites above baseline, best confirmed on imaging

Baseline imaging immediately before HSCT is recommended so these comparisons can be made.

Paediatric grading and what it changes

Grading uses more domains than in adults

- Transaminases: ALT, AST and glutamate dehydrogenase
- Duration of refractory thrombocytopenia: under 3 days, 3 to 7 days, over 7 days
- Ascites, coagulation and glomerular filtration rate
- Oxygen requirement and central nervous system function

The most severe category applies. Two or more of the marked criteria upgrade to very severe, and cumulative symptoms evolving within 48 hours predict severe disease.

Using EBMT criteria changed care

- Detection 8.9% versus 4.9% with modified Seattle or Baltimore criteria
- Shorter defibrotide courses
- Hospital stay shorter by a median of 12 days

Practice in Australasia

- Defibrotide is used more readily, and dose and duration are consistent across paediatric centres
- High-dose methylprednisolone is also used
- Access is less restricted than for adults

The four recommendations

1 Assess	Prospectively assess every HSCT recipient for SOS/VOD risk, and apply risk-modification strategies where feasible
2 Prevent	Give ursodeoxycholic acid prophylaxis to all HSCT recipients, from the start of conditioning to day +90
3 Diagnose	Establish diagnosis and severity with reference to the EBMT criteria wherever possible
4 Treat	Add defibrotide 25 mg/kg/day for 14 to 21 days to best supportive care in moderate or severe disease, weaning after response and ceasing at resolution

A model for society guidelines?

A niche topic that was widely read

Top 10%

of articles accessed in the Internal Medicine Journal

For a subspecialty topic in a general internal medicine journal

SOS/VOD sits in a narrow corner of transplant practice, yet the statement was read across the wider physician readership.

Focus did not limit the audience — it created one

Practical, well-scoped guidance gets used well beyond the subspecialty that wrote it

Scope discipline: what we did and did not take on

In scope

- Transplant and cellular therapy complications, and nothing wider
- Points where Australian and New Zealand factors change management: TGA and Pharmac approval, funding and access
- Local incidence data and documented variation between our centres

Deliberately left alone

- Not telling non-transplant physicians how to treat with IO/GO – rather consider the balance of risks
- Restating international guidance that needs no local adaptation
- Ground already covered well by other disease-focused groups

Focused, relevant and specific to our region's practice

A narrow remit is what made the recommendations actionable rather than aspirational

Who wrote it

Physicians
Adult and paediatric transplant clinicians

Nurses
Bedside recognition and day-to-day monitoring

Pharmacists
Dosing, washouts, interactions and access

Scientists
Disease biology and pharmacogenomics

Eighteen authors, drawn from adult and paediatric centres across Australia and New Zealand

Each contributed where their expertise sat. The statement covers dosing, monitoring, laboratory and clinical decision-making because the people who do that work were in the room.

Proposing the next statement

1. Take it to the Education Committee

The ANZTCT welcomes proposals for guidelines and position statements. Bring the idea to the education committee for consideration.

2. Bring the authors with it

Think about who your authorship group will be – consider people outside of your own profession and consider the broader region.

3. Fill a role no one else can

Choose questions rooted in transplant and cellular therapy practice, where local access and funding shape the answer.

If another group can answer it better, let them. If they cannot, it is ours to write.

Where the work still needs to be done

Prevention remains the most effective strategy we have

Biomarkers

Validated biomarkers to identify at-risk patients shortly after HSCT

Earlier treatment

The utility of defibrotide at earlier stages of severity, particularly moderate disease

New agents

New prophylactic and therapeutic options, and improved understanding of disease biology

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With thanks to all co-authors and to the ANZTCT

Thank you

Questions?