Infection in Mechanical Circulatory Support

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Relevant Financial Relationship Disclosure Statement

I will discuss off label use and/or investigational use of the following drugs/devices:
No

The following relevant financial relationships exist related to my role in this session: No

Background

- Mechanical circulatory support (MCS) is a well recognized treatment for advanced heart failure.
- Over the last decade the devices and strategies used for MCS have changed.
- Whilst infection rates have also changed, infection still remains a major source of adverse events (AE) in these patients.
- Understanding the epidemiology of the currently used MCS devices and strategies is essential to refine prevention strategies and reducing the incidence of AE infection in MSC patients.

Changes that influenced infection in MCS

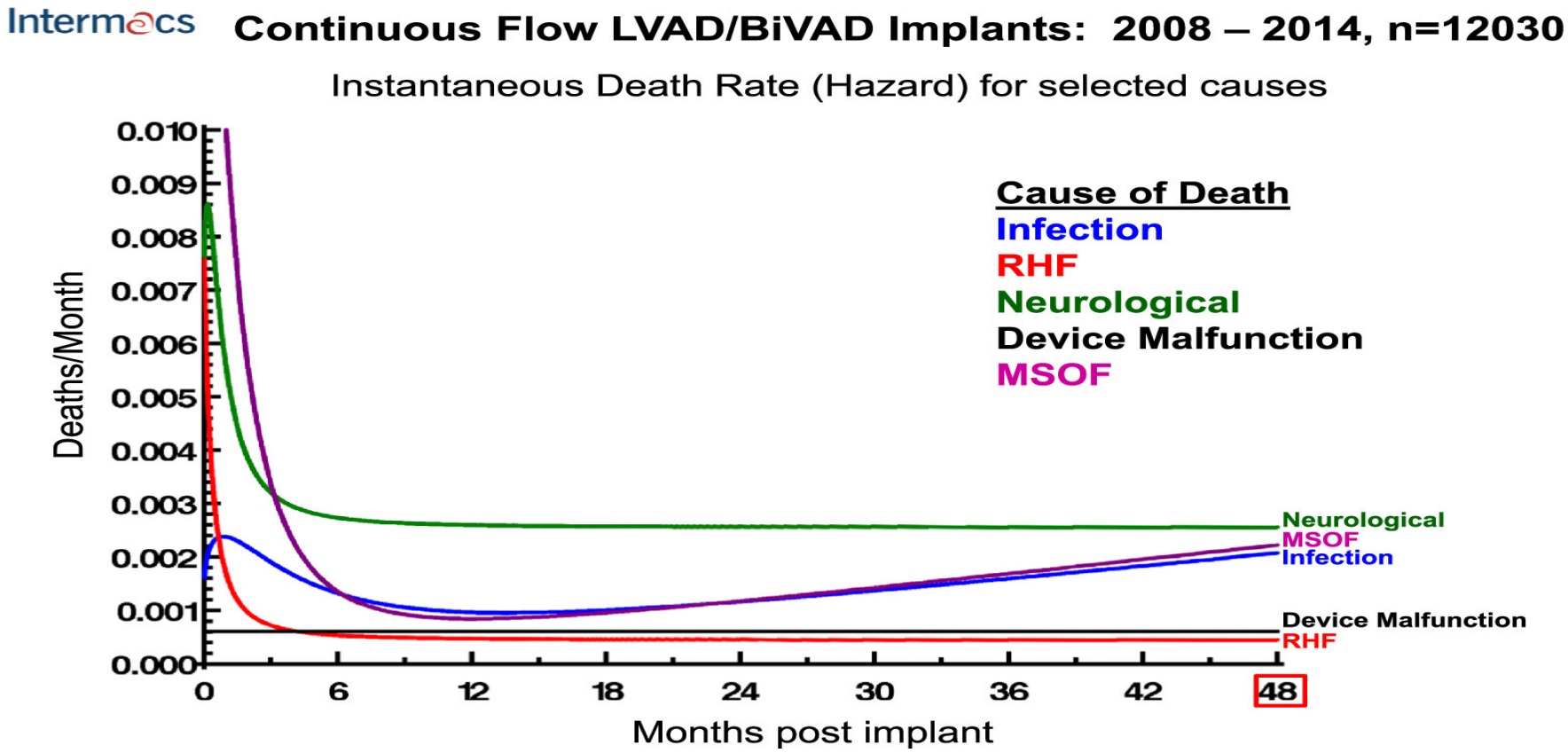
- Continuous flow devices replaced larger pulsatile flow pumps & currently represent 95% of all LVAD implants
  - Smaller pockets and driveline dimension associated with reduced infection rates
    - Kirklin JK et al. Fifth and Seventh INTERMACS and annual report. JHLT 2013 32(2):p141-56, JHLT 2015 34(12):p1495-504.

- LVAD use for Destination therapy (DT) has increased significantly
  - >50% were destination therapy
    - Seventh INTERMACS annual JHLT 2015 34(12):p1495-504, EUROMACS Eur J Cardiothoracic Surg. TM de By et al. 2015 47(5) p 770

Microbiology

- Etiology of infection has not changed over time
  - Bacterial infections predominate, early and late
  - Most common infection overall Gram-positive *S. aureus* & *S Epi* >50%, bacteria that colonize the skin, adhere to implants & create bioflims
  - Most common Gram-negative infection *P. aeruginosus* 22-28%
  - Fungal infection from 1-10%. *C. albicans* >70%
- MRSA, VRE, CRE infection rates will vary related to regional and institutional epidemiology

Gordon et Al Ann Thorac Surg 2001, Weyand et al Transplant proc 1997
Nienaber et al, CID 2013 Gordon RJ et al Circulation et al. 2013
Schaffer et al JHLT 2011, Sharma et al Ann Thorac Surg 2012

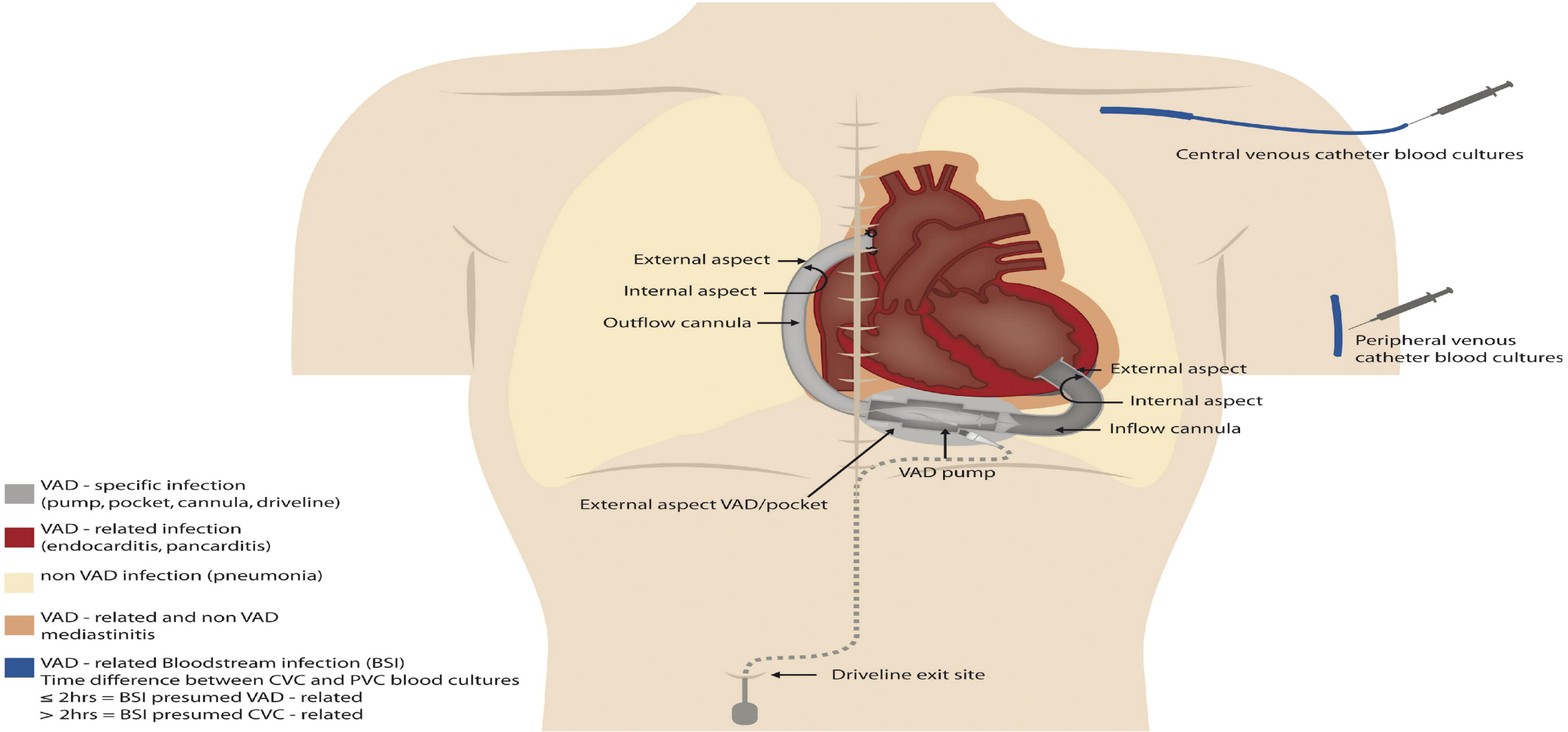


New ISHLT definitions of infection

Category	Location
VAD specific	Pump and/or cannula infection (includes pump interior from INTERMACS)
	Pocket Infection
	VAD drive line
VAD related	VAD related bacteraemia
	VAD related mediastinitis
	VAD related mediastinitis pocket
Non VAD related	Pulmonary/pneumonia
	Lines sepsis (includes both non VAD related line, non VAD related bacteraemia, other cause)
	UTI
	GI

Hannan MM et al JHLT 2011 30(4) p375-384

Definitions of infection in MCS patients-ISHLT consensus 2011



Hannan MM et al JHLT 2011 30(4) p375-384

The Epidemiology of Infection in Mechanical Circulatory Support from the IMACS database: January 2013-December 2015

Margaret Hannan[1], Rongbing Xie[2], Jennifer Cowger[3], Stephan Schueler[4], Theo de By[5], Anne Dipchand[6], Vivian Chu[7], Ryan Cantor[2], C. Koval[8], T. Krabatsch[9] , C. Hayward[10] James Kirklin[2]

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Outline of Study

I. Background/Specific Aims
II. Cohort
III. Baseline Summaries
IV. Methods
V. Analysis
VI. Conclusions

Specific Aims

- To examine the type, location and timeline of infections in patients receiving durable cardiac assist devices

Background - Endpoints*

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VAD specific	Pump and/or cannula infection (includes pump interior from INTERMACS)
	Pocket Infection
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* First major Infection

J Heart Lung Transplant. 2011 Apr;30(4):375-84

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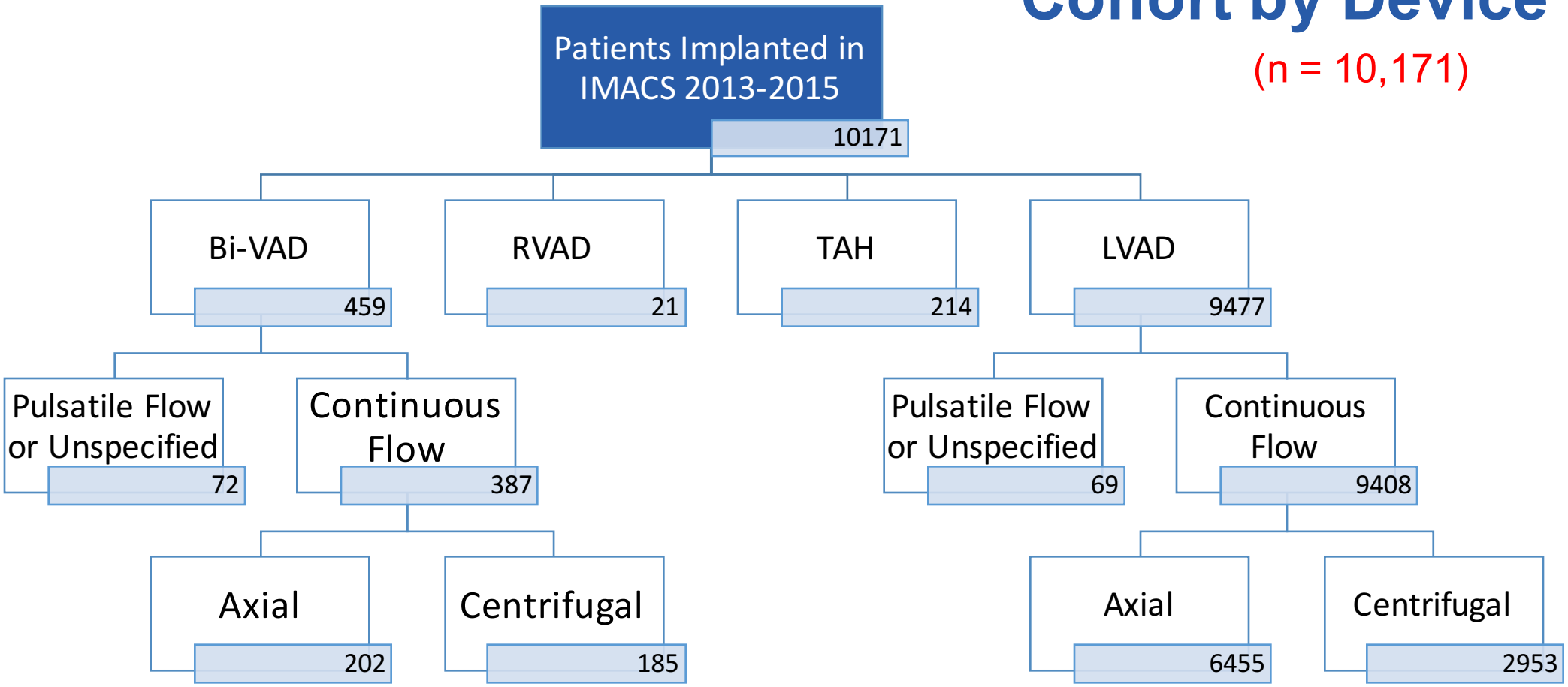
The Epidemiology of Infection

(Jan 1, 2013 - Dec 31, 2015, n = 10,171

Cohort by Device Type

(n = 10,171)



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Epidemiology of Infection

Baseline Characteristics

Characteristic	N=10,171
Male gender	8024 (78.9%)
Age at implant, years	
19-29	508 (4.99%)
30-49	2331 (22.9%)
50-69	6072 (59.9%)
70+	1240 (12.2%)
Device type	
BiVAD	459 (4.5%)
RVAD	21 (0.2%)
TAH	214 (2.1%)
LVAD	9477 (93.2)
INTERMACS category	
I	1707 (16.8%)
II	3444 (33.9%)
III	3194 (31.4%)
IV	1350 (13.3%)
V-VI	331 (3.3%)

Baseline Characteristics

Characteristic	N = 10,171
Device Strategy at the time of implant	
Bridge to transplant	3010 (29.6%)
Bridge to candidacy	2900 (28.5%)
Destination therapy	4261 (41.9%)

Outline of Study

I. Background/Specific Aims
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Methods

- INTERMACS Registry definitions for infection were used to categorize AE infections occurring in all MCS pts within the IMACS registry.

- The IMACS infection variables were mapped to the new ISHLT definitions for infection where feasible.

Outline of Study

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Number and Percent of All Patients Experiencing Major Adverse Events

Adverse Event	Patients Experiencing Event	Percent of all Patients
Bleeding	3,373	33
Infection	3,788	37
Neurological dysfunction	1,807	18
Respiratory failure	1,689	17
Device malfunction	1,261	12
Arterial non-CNS thromboembolism	124	1

The Epidemiology of Infection
(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

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The Epidemiology of Infection

Number of AE infection overall

Category	Location	N of Infection
VAD specific n=1756	Pump and/or cannula infection (includes pump interior from INTERMACS)	76
	Pocket Infection	224
	VAD drive line	1456
VAD related n=491	VAD related bacteraemia	228
	VAD related mediastinitis	238
	VAD related mediastinitis pocket	25
Non VAD related n=4041	Pneumonia	1533
	Lines sepsis (includes both non VAD related line, non VAD related bacteraemia, other cause)	1376
	UTI	1132

The Epidemiology of Infection

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The Epidemiology of Infection
(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

Microbiology of VAD-Specific Infection By Location

Location	Bacterial	Fungal	Unknown	Total
	N (%)	N (%)	N (%)	
Pump and/or cannula infection	66 (87%)	4 (5%)	6 (8%)	76
Pocket Infection	189 (84%)	7 (3%)	28 (13%)	224
VAD drive line	1234 (85%)	4 (0%)	214 (15%)	1456

The Epidemiology of Infection

(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

Microbiology of VAD-Related Infection By Location

Location	Bacterial	Fungal	Unknown	Total
	N (%)	N (%)	N (%)	
VAD related Bloodstream Infection	222 (97%)	4 (2%)	2 (1%)	228
VAD related mediastinitis	181 (76%)	18 (8%)	38 (16%)	238
VAD related mediastinitis pocket	21 (84%)	2 (8%)	2 (8%)	25

Microbiology of Non VAD-related Infection

Location	Bacterial	Fungal	Viral	Unknown	Total
	N (%)	N (%)	N (%)	N (%)	
Pulmonary/ pneumonia	1203 (78%)	107 (7%)	73 (5%)	146 (10%)	1533
Non-VAD-related BSI	1252 (91%)	81 (6%)	8 (1%)	34 (2%)	1376
UTI	1018 (90%)	71 (6%)	0 (0%)	39 (3%)	1132

Early and Late VAD-specific Infection Rates by Location

Location	Early infection (<3months) N (rate per 100 person-months)	Late infection (>3months) N (rate per 100 person-months)	P-value
Pump and/or cannula infection	24 (0.09)	52 (0.06)	0.14
Pocket infection	91 (0.34)	133 (0.14)	<0.01
VAD drive line	345 (1.28)	1111 (1.20)	0.30

The Epidemiology of Infection
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Early and Late VAD-related Infections Rates by Location

Location	Early infection (<3months) N (rate per 100 person-months)	Late infection (>3months) N (rate per 100 person-months)	P-value
VAD related BSI	59 (0.22)	169 (0.18)	0.21
VAD related Mediastinitis	169 (0.63)	69 (0.07)	<0.01
VAD related Mediastinitis pocket	15 (0.06)	10 (0.01)	<0.01

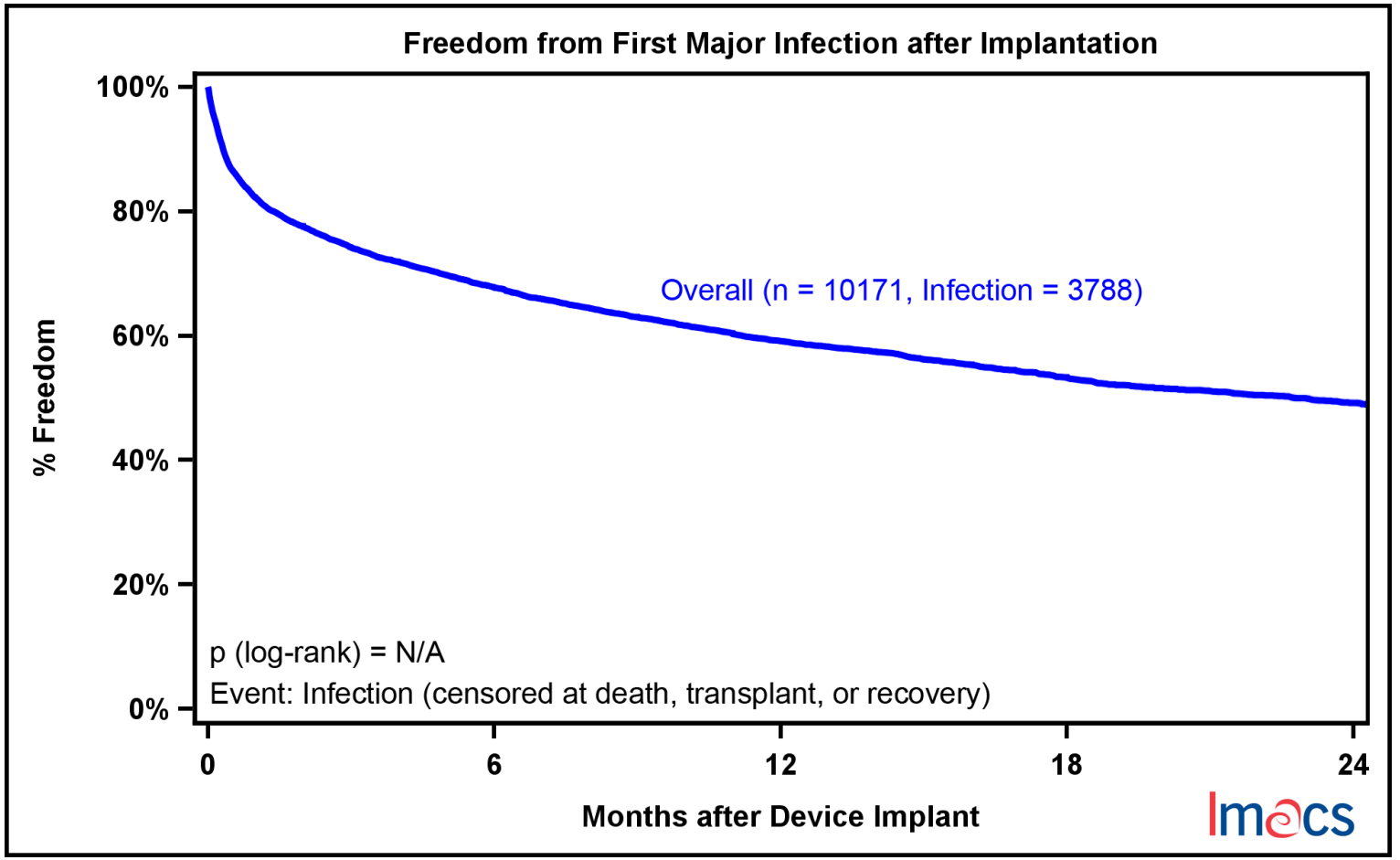
The Epidemiology of Infection
(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

Early and Late Non VAD-related Infection Rates by Location

Location	Early infection (<3months) N (rate per 100 person-months)	Late infection (>3months) N (rate per 100 person-months)	P-Value
Pulmonary/Pneumonia	1122 (4.18)	411 (0.45)	<0.01
Non-VAD-related BSI	594 (2.21)	782 (0.85)	<0.01
UTI	730 (2.72)	402 (0.44)	<0.01

The Epidemiology of Infection
(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

Freedom from First Major Infection after Implantation



Months after Device Implant	Freedom from Infection
1	82.2% (81.8%-82.6%)
3	74.2% (73.8%-74.7%)
6	67.8% (67.3%-68.3%)
12	59.1% (58.6%-59.7%)
18	53.3% (52.7%-53.9%)
24	49.2% (48.5%-49.9%)

The Epidemiology of Infection
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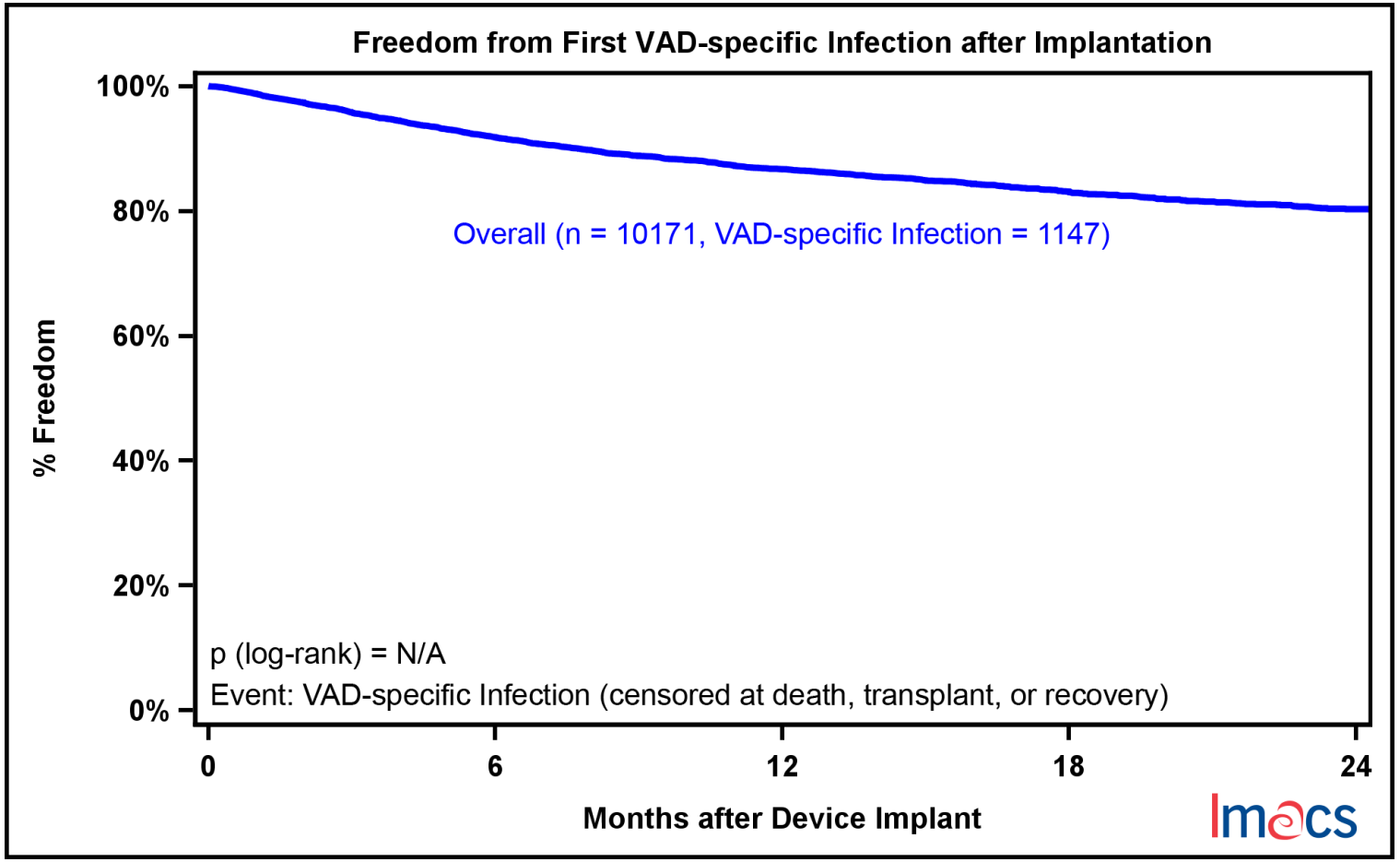
Freedom from First VAD-specific Infection after Implantation



Months after Device Implant	Overall
1	98.8% (98.7%-98.9%)
3	95.8% (95.6%-96.0%)
6	91.8% (91.5%-92.1%)
12	86.7% (86.3%-87.1%)
18	83.1% (82.6%-83.6%)
24	80.3% (79.7%-80.9%)

The Epidemiology of Infection
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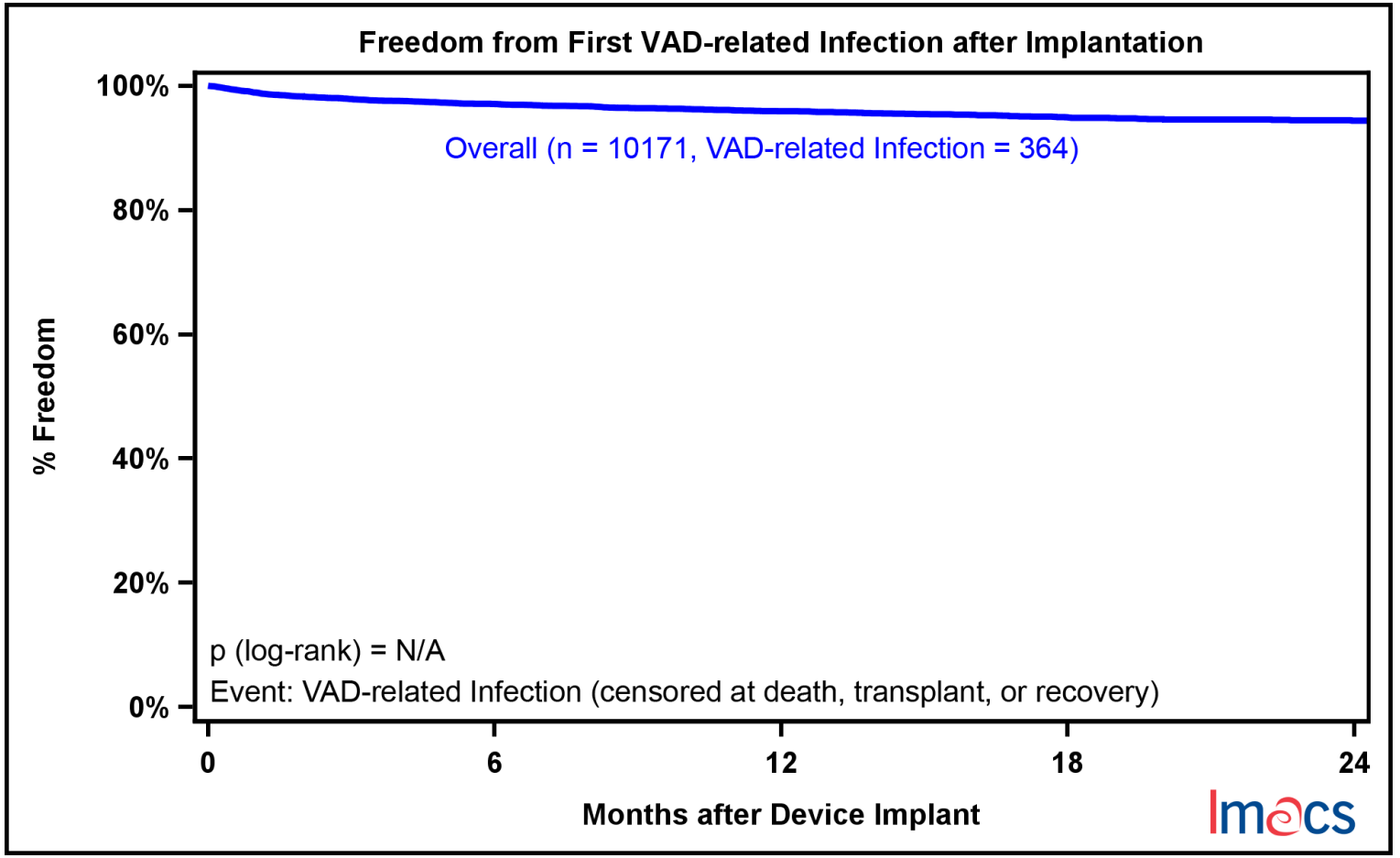
Freedom from First VAD-related Infection after Implantation

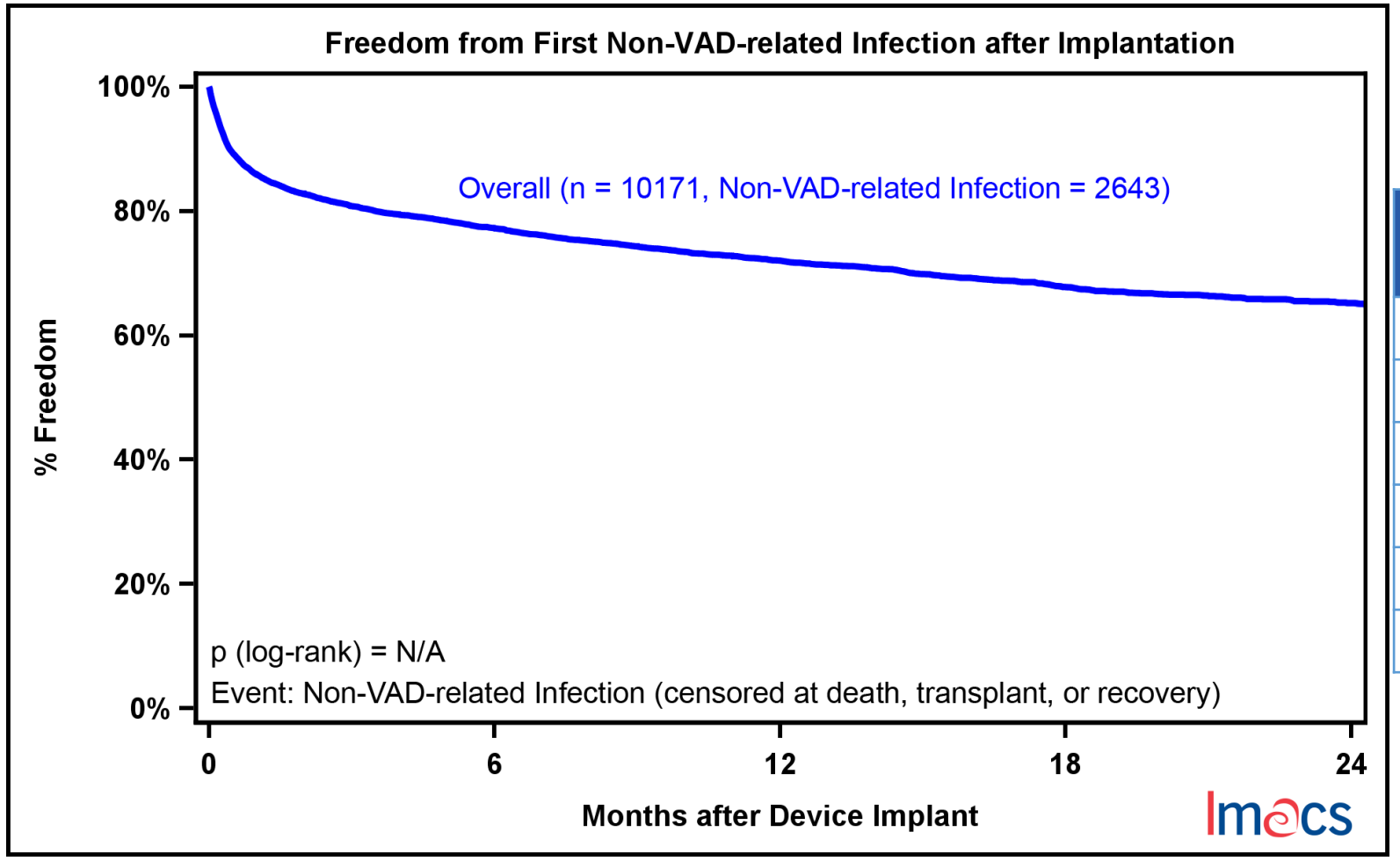


Months after Device Implant	Overall
1	98.9% (98.8%-99.0%)
3	97.9% (97.7%-98.0%)
6	97.1% (96.6%-97.3%)
12	95.9% (95.7%-96.1%)
18	94.9% (94.6%-95.2%)
24	94.4% (94.0%-94.7%)

The Epidemiology of Infection

(Jan 1, 2013 - Dec 31, 2015, n = 10,171)

Freedom from First Non-VAD-related Infection after Implantation



Months after Device Implant	Overall
1	85.9% (85.6%-86.3%)
3	80.8% (80.4%-81.2%)
6	77.3% (76.8%-77.7%)
12	72.0% (71.5%-72.5%)
18	67.8% (67.2%-68.3%)
24	65.2% (64.5%-65.8%)

The Epidemiology of Infection

International IMACS MCS infection rates

Category	Location	Infection rates -100 person mts Early (<3 mts)	Late (>3 mts)	P-Value
VAD specific	Pump and/or cannula infection (includes pump interior from INTERMACS)	24 (0.09)	52 (0.06)	0.14
	Pocket Infection	91 (0.34)	133 (0.14)	<0.01
	VAD drive line	345 (1.28)	1111 (1.20)	0.30
VAD related	VAD related bacteraemia	59 (0.22)	169 (0.18)	0.21
	VAD related mediastinitis	169 (0.63)	69 (0.07)	<0.01
	VAD related mediastinitis pocket	15 (0.06)	10 (0.01)	<0.01
Non VAD related	Pneumonia	1122 (4.18)	411 (0.45)	<0.01
	Lines sepsis (includes both non VAD related line, non VAD related bacteraemia, other cause)	594 (2.21)	782 (0.85)	<0.01
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The Epidemiology of Infection

Conclusions

Non VAD-related infection, represent the largest category of MCS infection overall with pneumonia being the leading infection site followed by BSI, and UTI.

All AE infection in MCS patients occurred more frequently in the 3 months post implant irrespective of type or location of infection.

Drive-line infection still remains the most common type of VAD specific infection and most frequently reported in the first 3 months post implant.

Antimicrobial Surgical Prophylaxis in MCS Implant Surgery and Surgical Site Infection

IMACS January 2013 through to December 2015

Margaret Hannan[1], Rongbing Xie[2], Shimon Kusne[3], Chris Merry[4], Paolo Grossi[5], Valintina Storo[6], Cumara Sivathasan[7], Mandeep Mehra[8], Ulrich Jorde[9], Ivan Netuka[10], Shirish Huprikar[11], James Kirklin[2]

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Antimicrobial Surgical Prophylaxis in MCS

Specific Aims

- To compare SSI, VAD specific and VAD related infection in patients (pts) following MCS implant surgery using different antimicrobial combinations at time of implant

- To assess the types and durations of antimicrobial regimens

Background – Cohort(s) Definition

- MCS patients implanted from January 1, 2013 through to December 31, 2015 (n=161) in 20 IMACS individual hospitals

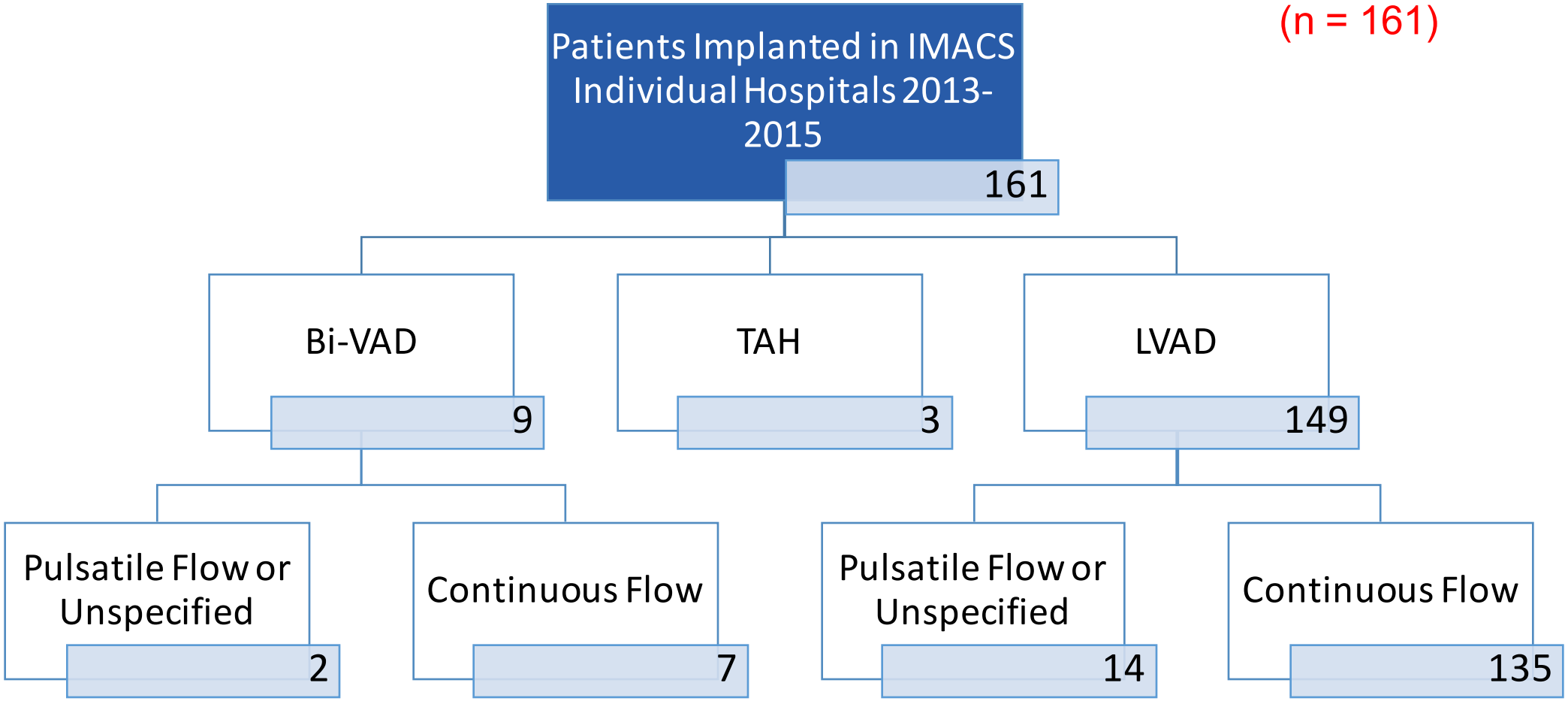
Background – Endpoints

- Surgical site infection including wound infection, sternotomy infection, mediastinitis

Antimicrobial Surgical Prophylaxis in MCS

Cohort by Device Type

(n = 161)



Antimicrobial Surgical Prophylaxis in MCS

(Jan 1, 2013 - Dec 31, 2015, n = 131)

Pre-implant Use of Antimicrobial Prophylaxis Regimens

Commonest antimicrobial combinations	N (%)
Van + cefazolin +fluconazole	34 (26%)
Van + cipro +fluconazole	24 (18%)
Van + cefazolin	6 (5%)
Van + cipro	2 (2%)
Vanco + other	31 (24%)
Van only	7 (5%)

Only 131 patients had information on regimen use; One patient had Van + cefazolin + Cipro + fluconazole and was presented in both combinations

Antimicrobial Surgical Prophylaxis in MCS

(Jan 1, 2013 - Dec 31, 2015, n = 131)

Pre-implant Use of Antimicrobial Prophylaxis Regimens

Commonest antimicrobial combinations	N	Duration 24hrs (%)	Duration 48hrs (%)	Duration 72hrs (%)
Van + cefazolin +fluconazole	34	18 (53%)	2 (6%)	14 (30%)
Van + cipro +fluconazole	24	10 (42%)	3 (12%)	11 (46%)
Van + cefazolin	6	4 (67%)	2 (33%)	0 (0%)
Van + cipro	2	1 (50%)	0 (0%)	1 (50%)
Vanco + other	31	6 (19%)	2 (7%)	23 (74%)
Van only	7	2 (28.5%)	3 (43%)	2 (28.5%)

Only 131 patients had information on regimen use; One patient had Van + cefazolin + Cipro + fluconazole and was presented in both combinations

Antimicrobial Surgical Prophylaxis in MCS

(Jan 1, 2013 - Dec 31, 2015, n = 131)

Pre-implant Use of Antimicrobial Prophylaxis Regimens[1] and Subsequent First Surgical Site Infection[2]

Commonest antimicrobial combinations	N	SSI <30 days	SSI <90 days	Later SSI
Van + cefazolin +fluconazole	34	0	1 (3%)	2 (6%)
Van + cipro +fluconazole	24	0	2 (8%)	0
Van + cefazolin	6	1 (17%)	0	1 (17%)
Van + cipro	2	0	1 (50%)	1 (50%)
Vanco + other	31	1 (3%)	1 (3%)	2 (6%)
Van only	7	0	1 (14%)	0

[1] Only 131 patients had information on regimen use; One patient had Van + cefazolin + Cipro + fluconazole and was presented in both combinations

[2] Surgical site infection (SSI) including wound infection, sternotomy infection, mediastinitis

Antimicrobial Surgical Prophylaxis in MCS

Conclusions

- This multicenter, international study shows variation both in choice of antimicrobial surgical prophylaxis regimens and durations used across IMACS registry hospitals.

- The most common antimicrobial regimen was vanco, cefazolin, and fluconazole for 24 hours.

Overall conclusion

Conclusions

MCS programs should focus IPC strategy and resources on reducing Non VAD-related infection in the first 3 months post implant.

Reducing pneumonia, BSI, and UTI's in the first 3 months will have a significant impact on overall incidence of infection in MCS pts.

The IMACS multinational and multicenter registry provides global international MCS infection rates that can by used by all MCS programs to benchmark their local infection rates.

Acknowlegements

UAB

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Sharmene Smith

Ryan Cantor

INTERMACS team

ISHLT IMACS Committee

Other studies ongoing

IMACS Recruiting research project and enrolling key hospitals internationally to participate and collaborators

www.imacs.uab