Improving Indigenous Kidney Transplant Outcomes Workshop Darwin 14-15 October 2013

Infectious complications of renal transplantation in Australian contemporary urban settings

State of the art and emerging issues

David Looke FRACP FRCPA MMedSci
Princess Alexandra Hospital
Woolloongabba
Queensland

Advances in Transplantation

- Optimal tissue typing and matching
- Better individualized immunosuppressive regimens
- Careful donor selection and good preparation of recipient (particularly eradication of treatable infection beforehand)
- Impeccable surgical technique
- Prevention of infection and prompt diagnosis and treatment when it arises

Marty FM Rubin RH Transpl Int 2006 (19) 2-11)

Advances in Transplantation

- Optimal tissue typing and matching
- Better individualized immunosuppressive regimens
- Careful donor selection and good preparation of recipient (particularly eradication of treatable infection beforehand)
- Impeccable surgical technique
- Prevention of infection and prompt diagnosis and treatment when it arises

Marty FM Rubin RH Transpl Int 2006 (19) 2-11)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Infectious Diseases Physicians can now sit at the transplanter's table

Infections and Transplantation

$$\text{Infection} \sim \frac{\text{inoculum X virulence}}{\text{host resistance}}$$

Infections and Transplantation

- Source of organisms:
  - Organ /Donor derived
    - Herpes viruses
    - Tuberculosis
    - LCM
    - CMV
    - EBV
    - Gram negatives
  - Host derived
    - CMV
    - EBV
    - S aureus
    - E coli
    - Pseudomonas
    - Tuberculosis

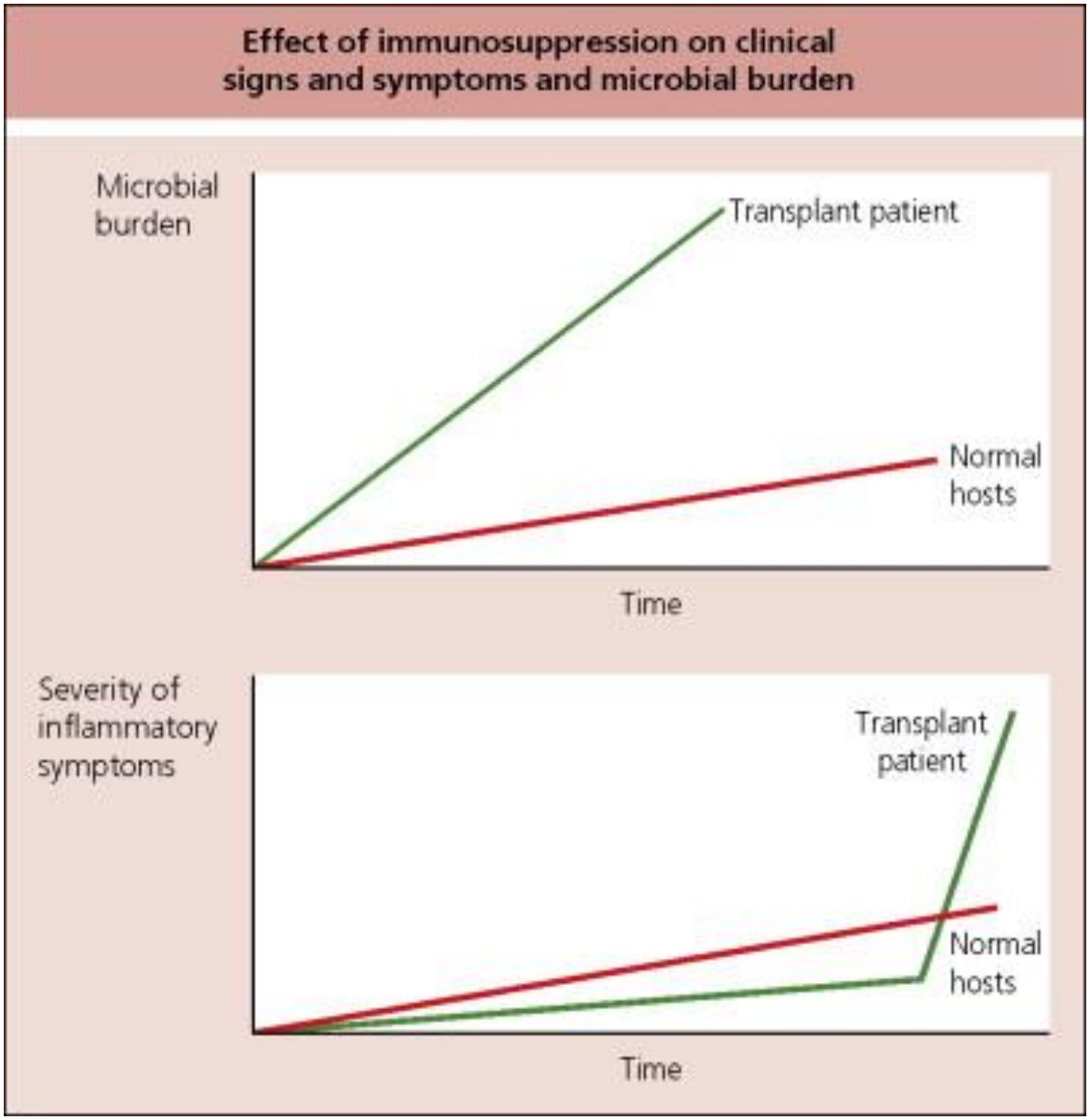
- Cross infection from other humans:
- varicella
- respiratory viruses
- MROs
- Tuberculosis

- Environmental
  - Cryptococcus
  - Legionella
  - Aspergillus

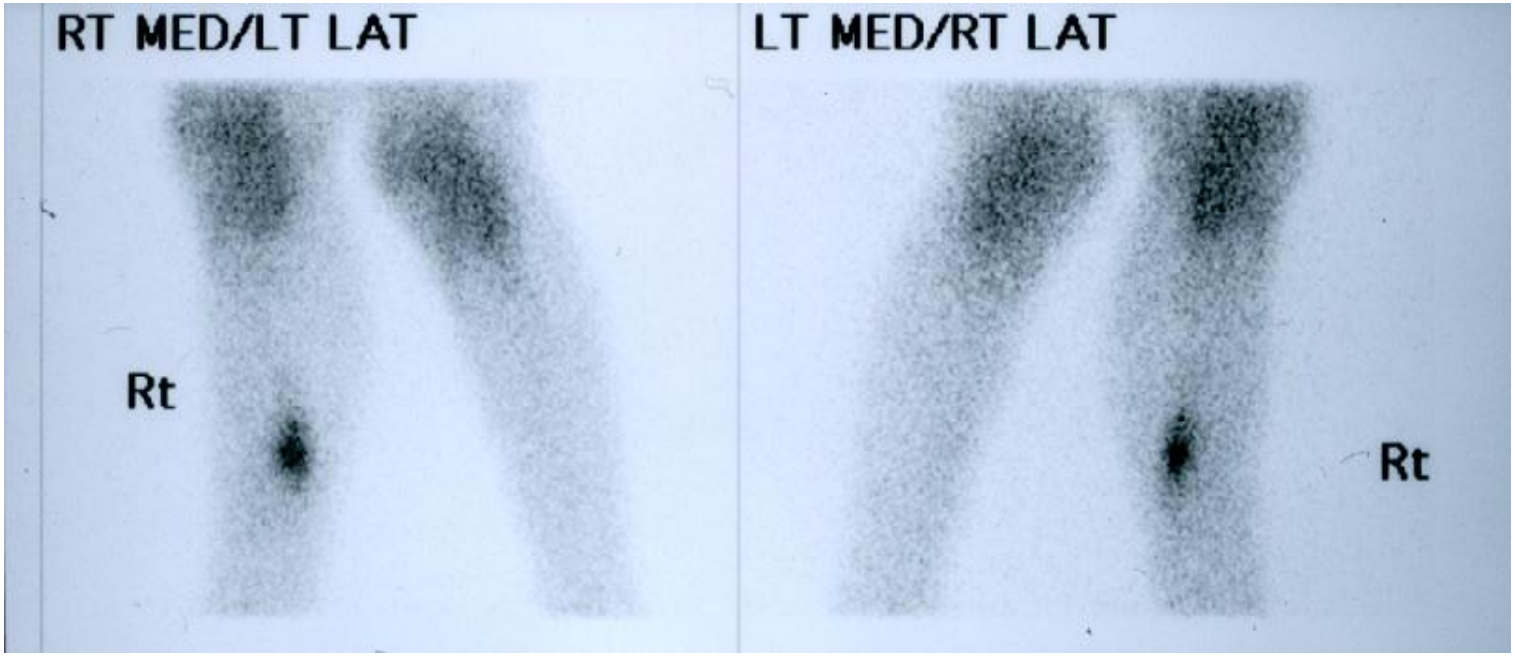
- Zoonotic
  - salmonellosis

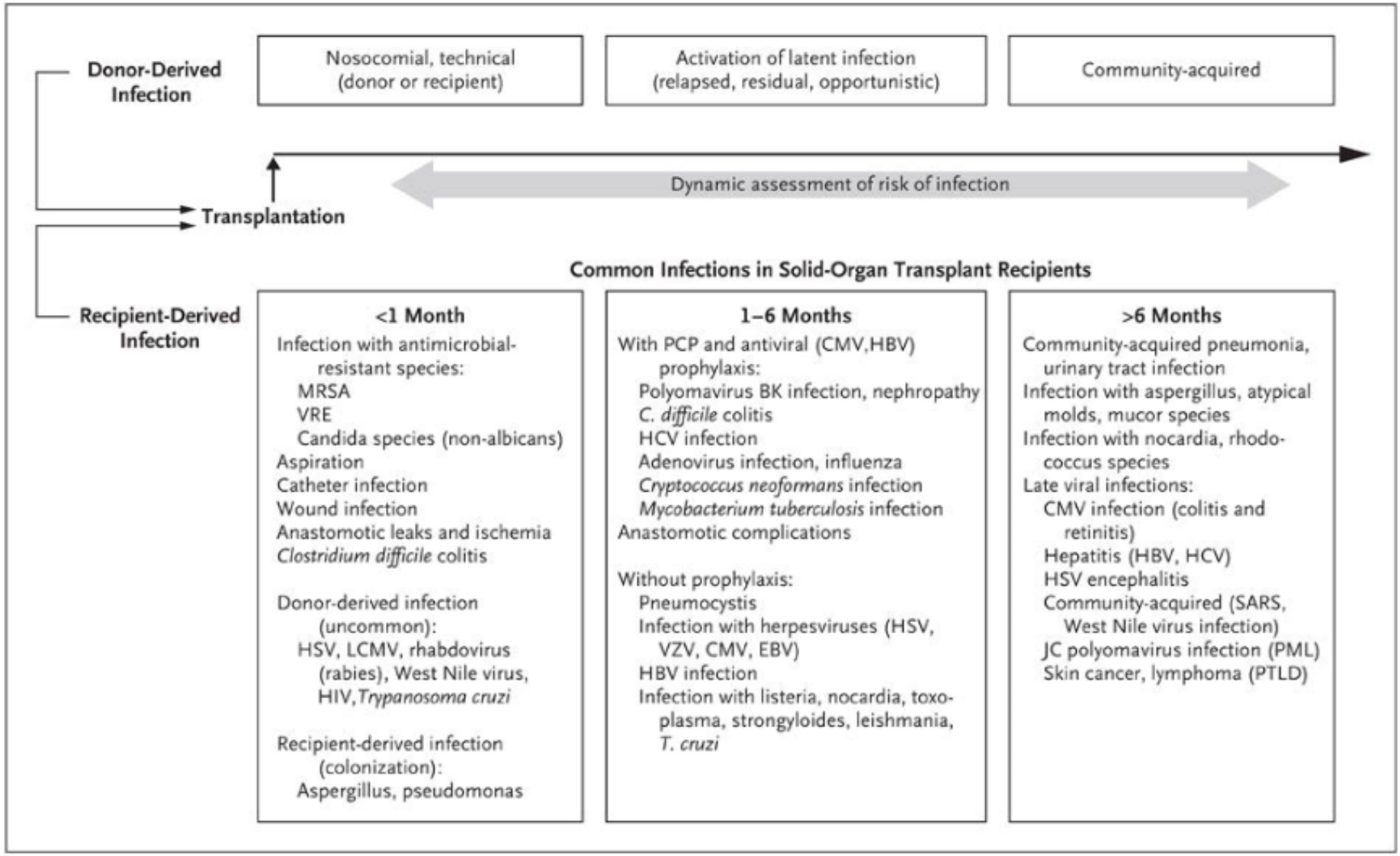
Infections and Transplantation

- Net state of Immunosuppression
  - Surgery
  - Immunosuppressive agents
  - Immunosuppressive infection (CMV)
  - Nutrition
- Inoculum
  - Contaminated organ
  - Bacteriuria
  - Environmental burden (aspergillus)
- Virulence
  - True pathogens (varicella, Mycobacterium tuberculosis,)
  - Opportunists (C.albicans, CMV, Cryptococcus)



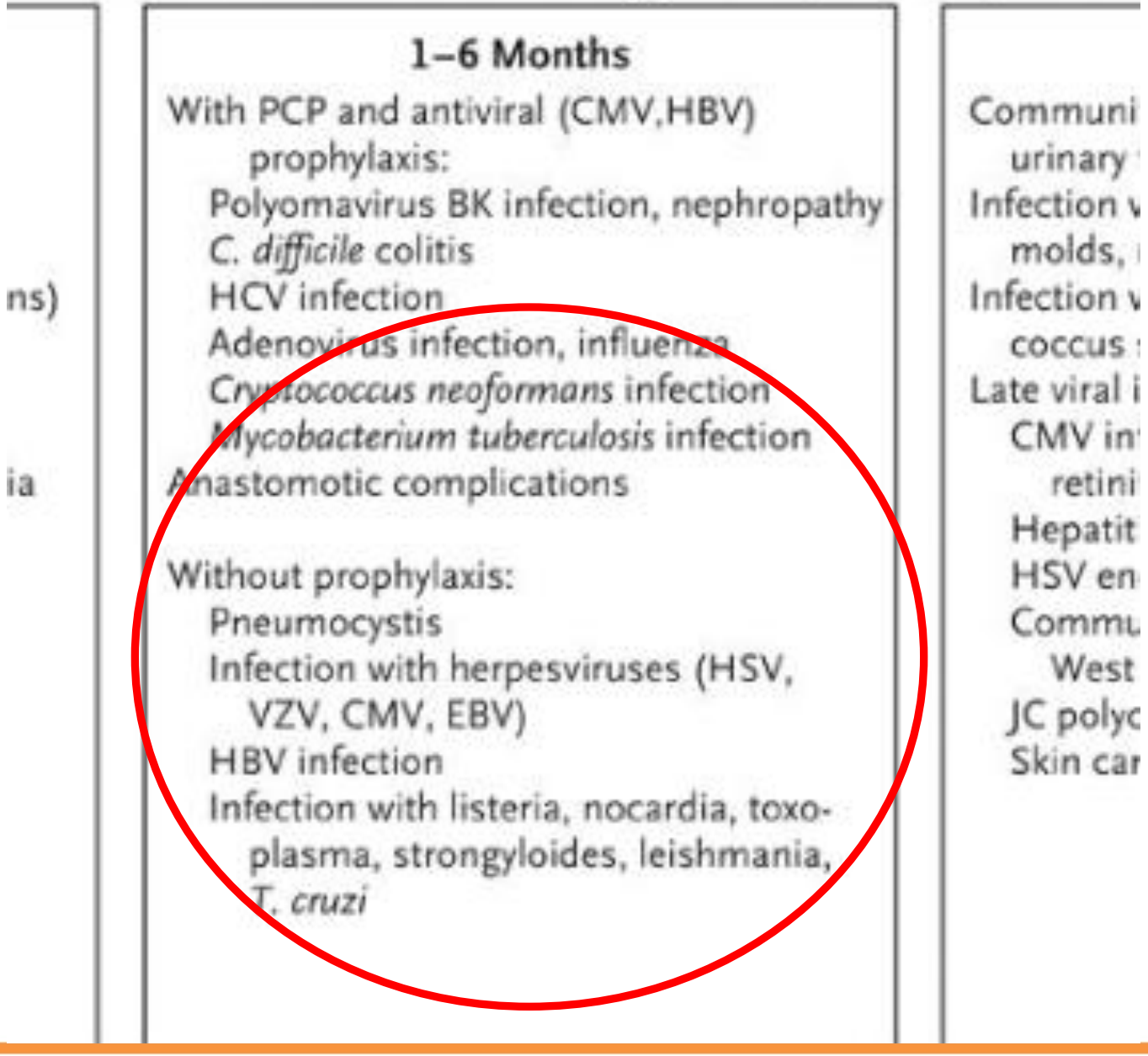
When infected, immunosuppressed patients vary in their clinical response with reduced or altered signs, symptoms and pathology testing, so diagnosis may be delayed creating a large organism burden


RT MED/LT LAT
Rt
LT MED/RT LAT
Rt



Fishman J NEJM 2007; 357:2601

Common Infections in Solid-Organ Transplant Recipients



ns)

ia

1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:
- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
- HCV infection
- Adenovirus infection, influenza
- *Cryptococcus neoformans* infection
- *Mycobacterium tuberculosis* infection

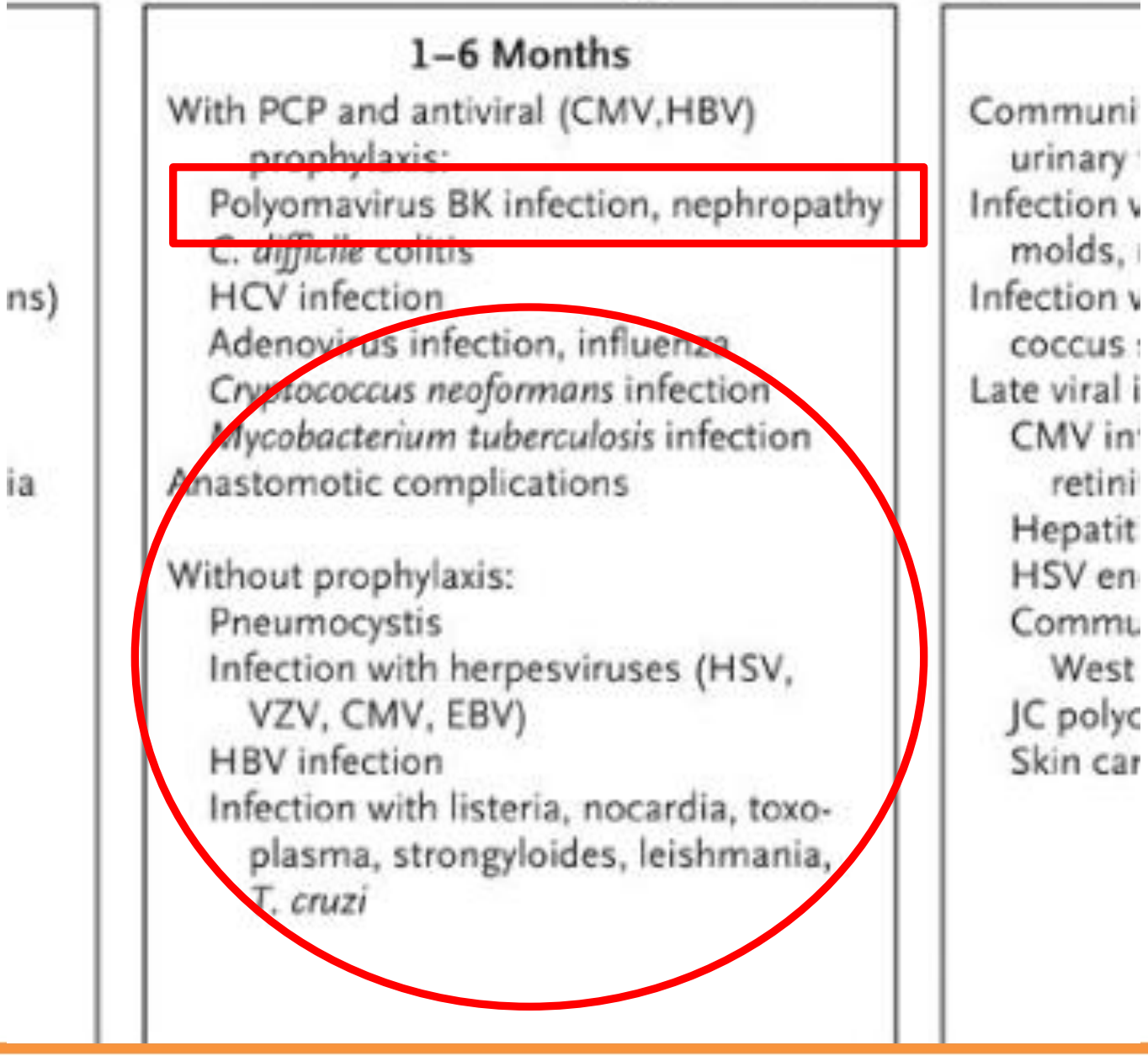
Anastomotic complications

Without prophylaxis:
- Pneumocystis
- Infection with herpesviruses (HSV, VZV, CMV, EBV)
- HBV infection
- Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

Communi
urinary
Infection v
molds,
Infection v
coccus
Late viral i
CMV in
retini
Hepatit
HSV en
Commu
West
JC polyc
Skin car

Fishman J NEJM 2007; 357:2601

Common Infections in Solid-Organ Transplant Recipients



ns)

ia

1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:

- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
- HCV infection
- Adenovirus infection, influenza
- *Cryptococcus neoformans* infection
- *Mycobacterium tuberculosis* infection

Anastomotic complications

Without prophylaxis:

- Pneumocystis
- Infection with herpesviruses (HSV, VZV, CMV, EBV)
- HBV infection
- Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

Communi
urinary
Infection v
molds,
Infection v
coccus
Late viral i
CMV in
retini
Hepatit
HSV en
Commu
West
JC polyc
Skin car

Fishman J NEJM 2007; 357:2601

Common Infections in Solid-Organ Transplant Recipients

<1 Month

Infection with antimicrobial-resistant species:
- MRSA
- VRE
- Candida species (non-albicans)

Aspiration
Catheter infection
Wound infection
Anastomotic leaks and ischemia
Clostridium difficile colitis

Donor-derived infection (uncommon):
- HSV, LCMV, rhabdovirus (rabies), West Nile virus, HIV, *Trypanosoma cruzi*

Recipient-derived infection (colonization):
- Aspergillus, pseudomonas

1–6 Months

With PCP and antiviral (CMV,HBV) prophylaxis:
- Polyomavirus BK infection, nephropathy
- *C. difficile* colitis
- HCV infection
- Adenovirus infection, influenza
- *Cryptococcus neoformans* infection
- *Mycobacterium tuberculosis* infection

Anastomotic complications

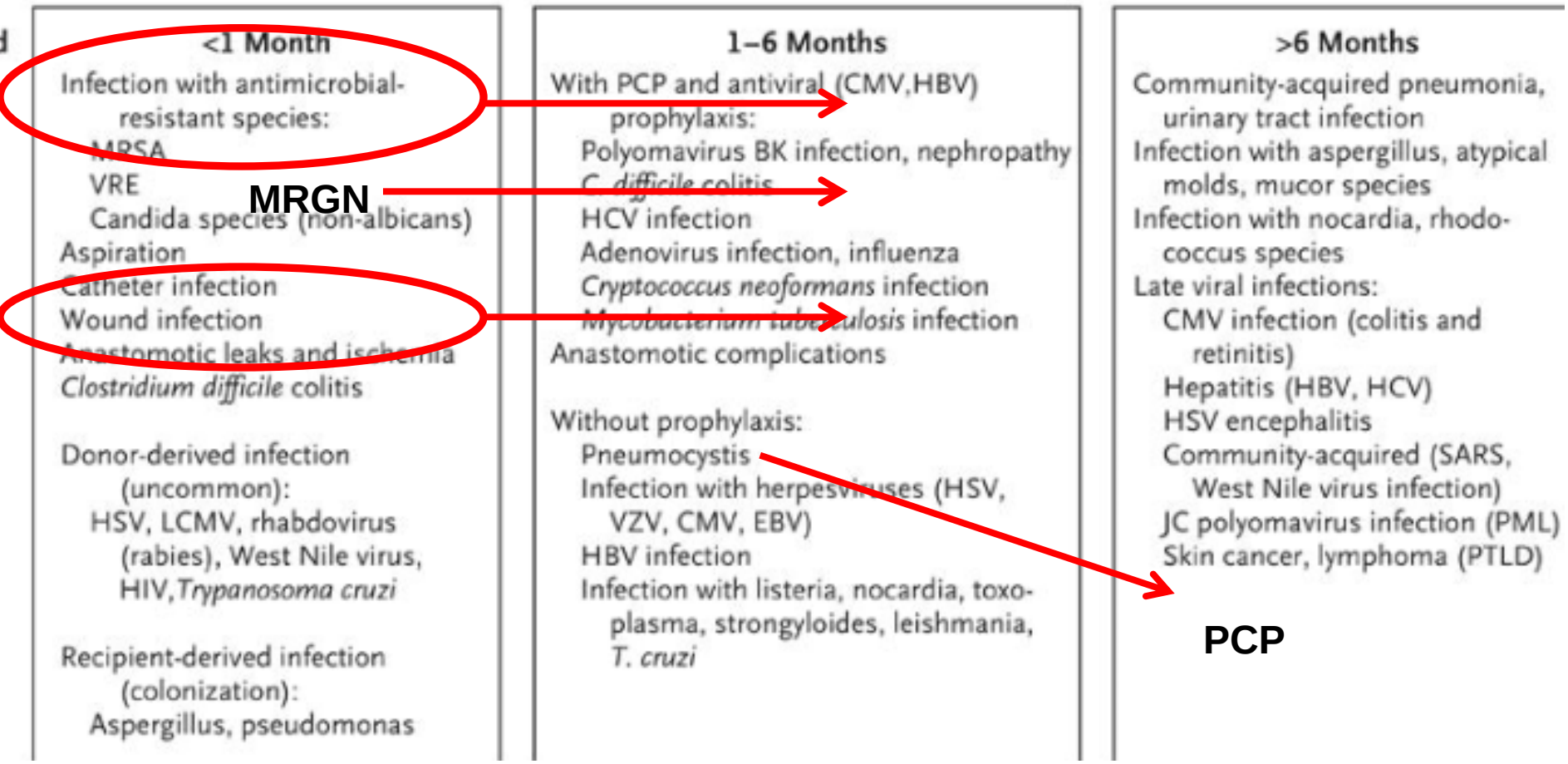
Without prophylaxis:
- Pneumocystis
- Infection with herpesviruses (HSV, VZV, CMV, EBV)
- HBV infection
- Infection with listeria, nocardia, toxoplasma, strongyloides, leishmania, *T. cruzi*

>6 Months

Community-acquired pneumonia, urinary tract infection
Infection with aspergillus, atypical molds, mucor species
Infection with nocardia, rhodococcus species
Late viral infections:
- CMV infection (colitis and retinitis)
- Hepatitis (HBV, HCV)
- HSV encephalitis
- Community-acquired (SARS, West Nile virus infection)
- JC polyomavirus infection (PML)
- Skin cancer, lymphoma (PTLD)

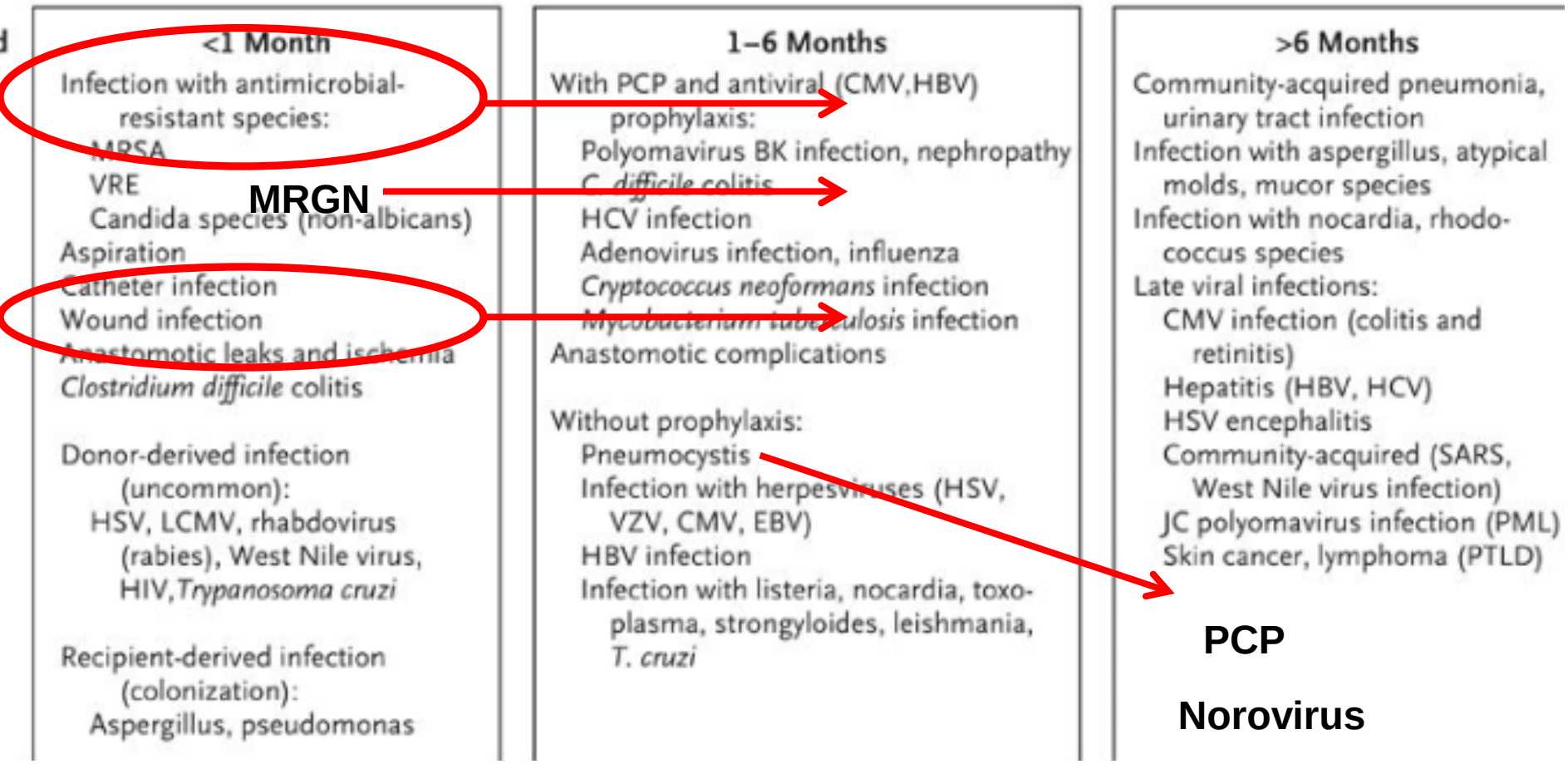
Fishman J NEJM 2007; 357:2601

Common Infections in Solid-Organ Transplant Recipients



Fishman J NEJM 2007; 357:2601

Common Infections in Solid-Organ Transplant Recipients



Fishman J NEJM 2007; 357:2601

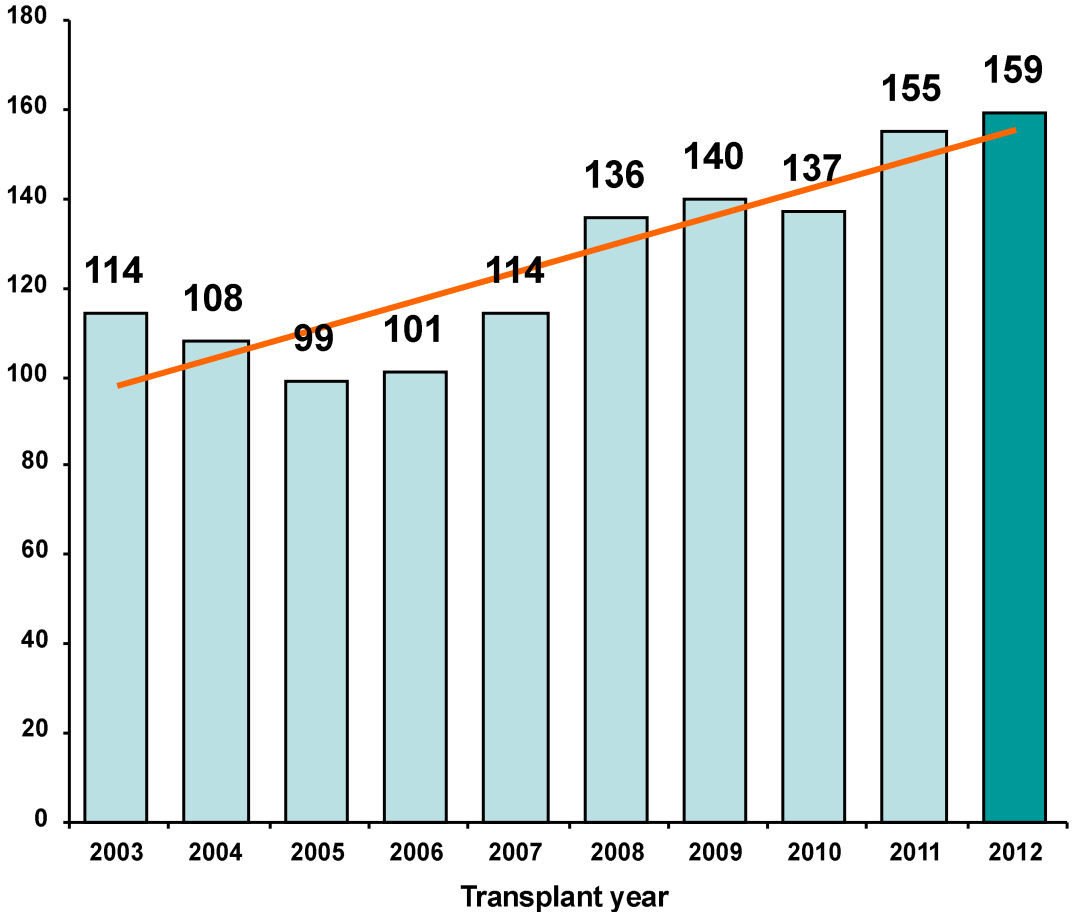
QRTS Snapshot Summary

Total number of reported transplants

3562

First transplant date: 13/09/1969

Last transplant date: 31/12/2012

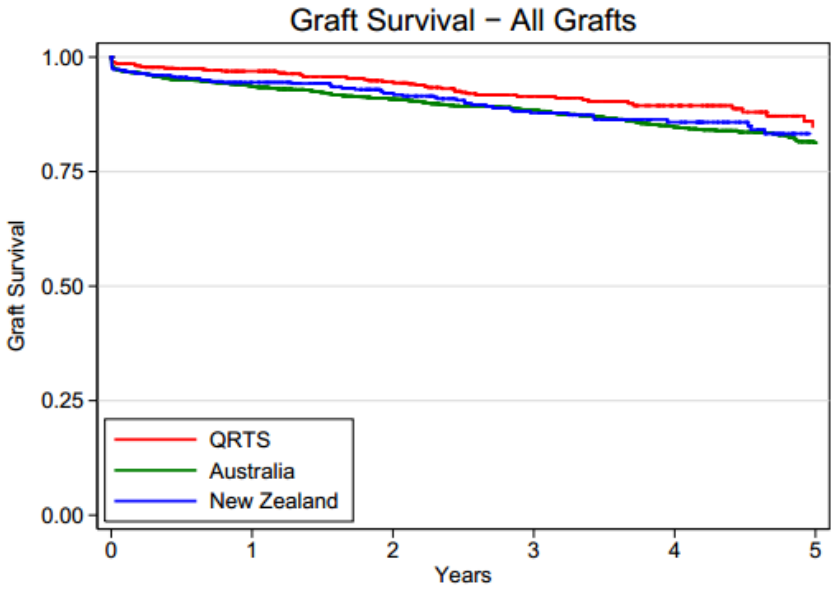


Graft Survival of all grafts

Graft survival is analysed from transplant until death, return to dialysis or most recent date of follow-up.

Table 16: Graft survival of all grafts.

	QRTS		Australia		New Zealand	
Time	n	% Survival (95% CI)	n	% Survival (95% CI)	n	% Survival (95% CI)
0	676	100.0	2975	100.0	527	100.0
3 months	634	97.8 (96.3-98.6)	2717	96.3 (95.6-96.9)	483	96.2 (94.1-97.5)
6 months	593	97.4 (95.9-98.4)	2556	95.0 (94.2-95.8)	452	95.6 (93.4-97.0)
1 year	527	96.9 (95.3-98.0)	2263	93.6 (92.7-94.5)	407	94.5 (92.1-96.2)
2 years	395	94.4 (92.1-96.0)	1684	90.8 (89.6-91.9)	316	92.1 (89.2-94.2)
3 years	282	91.4 (88.5-93.6)	1199	88.4 (87.0-89.7)	221	87.8 (84.1-90.7)
4 years	169	89.4 (85.9-92.1)	712	84.7 (82.9-86.3)	141	85.8 (81.5-89.1)
5 years	68	84.7 (78.9-89.1)	349	81.3 (78.9-83.4)	62	83.3 (78.1-87.4)



Source: ANZDATA Analysis (2006 - 2011)

Infections in Renal Transplantation

- So, what is happening in Australia?
- Are data on infection diagnoses and outcomes being systematically collected?
- Registry data does not include infectious disease
- Indirect data may be all that is available
  - Infection control surveillance
  - Outbreaks
  - Laboratory data
  - Special projects

Surgical Site Surveillance

Surgical Site Infections by Procedure

Princess Alexandra Hospital

Date Range: 01/01/2000 to 30/04/2013

Speciality	No. of procedures	Inhospital Infection				Post Discharge Infection	
		Superficial:	Deep Incis./Organ Sp.:	Total:	Rate:	Deep Incis./Organ Sp.:	Total:
Renal transplant	1,489	3	6	9	0.60%	8	17

Microbiology recorded:

No swab	16 (62%)
MRSA	5(19%)
MSSA	2(8%)
Klebsiella	1
Ecoli	1
Candida	1

Surgical Site Infection (SSI) Surveillance
PAH renal Transplant Unit 2008-April 2013

Years	Urology transplant	In-hospital SSI			Post discharge SSI		Total complex SSI	
	Total operations	Superficial	Complex	Rate	Complex	Rate	Complex	Rate
2008	132	0	0	0.00%	1	0.80%	1	0.80%
2009	124	0	1	0.80%	0	0.00%	0	0.00%
2010	125	0	0	0.00%	2	1.60%	2	1.60%
2011	139	0	0	0.00%	0	0.00%	0	0.00%
2012	142	0	1	0.70%	1	0.70%	2	1.40%
2013 to April	**53**	**0**	**0**	**0.00%**	**0**	**0.00%**	**0**	**0.00%**
Total (2008-2013 April)	*715*	*0*	*2*	*0.28%*	*4*	*0.56%*	*5*	*0.70%*

Renal Transplant

Surgical Antibiotic Prophylaxis Guidelines

PRE-OPERATIVE CONSIDERATIONS

Drug administration

- Slow IV bolus – should be given ≤ 60 minutes before skin incision (ideally at 30 minutes). Administration after skin incision or > 60 minutes before incision reduces effectiveness
- IV infusion – should be timed to end ≤ 30 minutes before skin incision

Pre-existing infections (known or suspected) – if present, use appropriate treatment regimen instead of prophylactic regimen for procedure. Doses should be scheduled to allow for re-dosing just prior to skin incision.

PROPHYLAXIS REGIMEN

Procedures	First line regimen	Alternative (Penicillin hypersensitivity)
Renal Transplant	**Piperacillin / Tazobactam 4.5g IV** infused over 30 minutes before incision	**Vancomycin 1g IV** infused over 100 minutes before incision, (**1.5g IV** for patients > 80 kg infused over 150 minutes) plus **Aztreonam 2g IV** bolus over 5 minutes before incision
Removal of Tenckhoff	**Treat exit site infection if present according to culture results, otherwise no antibiotics required**	
Removal of Stent	**Treat UTI if urine cultures positive. Nil antibiotics required if urine cultures negative.**	

MRSA COLONISATION

Patients with a history of MRSA colonisation or infection

ADD

Vancomycin 1g IV infused over 100 minutes before incision (**1.5g IV** for patients > 80 kg infused over 150 minutes)

VRE COLONISATION

Patients with VRE colonisation or infection, consider adding

Teicoplanin 800mg IV (single dose only) (1200mg IV for patients > 100 kg) if

- Bowel is entered
- Prosthetic material placement
- Instrumentation of urinary tract and VRE present in urine

(Vancomycin is not required if concurrently MRSA colonised)

DURATION OF PROPHYLAXIS

All perioperative prophylaxis is a single dose at induction of anaesthesia. Treatment of active infection requires a significant treatment course of appropriate antibiotics.

Urine Culture Isolates.
Renal Transplant Unit PAH 2008-Oct 2013

Organism	**Number of isolates**	**% Total Organisms**
E.coli	149	35%
Klebsiella	84	20%
Enterococcus	55	13%
Pseudomonas	35	8%
ESCAPPM	33	8%
Candida	32	7%
Proteus	18	4%
Grp B Strep	7	2%
Other GP	6	1%
Other GNB	3	1%
Salmonella	2	0.5%
S.aureus	2	0.5%
Haemophilus	1	0.2%
Total organisms	**427**	

Urine Culture Isolates.
Renal Transplant Unit PAH 2008-Oct 2013

Pathogen	No. of Isolates	%Sensitive										
		AMP	AUG	NIT	CRO	SXT	TMP	GEN	TAZ	NOR	CIP	MER
E.coli	149	38%	69%	93%	88%	60%	52%	94%	87% (99/113)	85%	87%	100%
Klebsiella	84	0%	88%	8%	92%	75%	74%	92%	94% (72/77)	89%	88%	100%
Pseudomonas	35							97%	100% (31/31)	100%	97%	100%
ESCAPPM	33	0%	0%	33%	55%	67%	64%	85%	57% (17/30)	88%	88%	100%
Proteus	18	67%	72%	0%	89%	89%	89%	100%	100% (14/14)	100%	100%	100%
Salmonella	2	100%	100%	100%	100%	100%	100%	100%		100%	100%	100%
Haemophilus	1	100%	100%		100%	100%						
Total	**322**											

Pathogen	No. of Isolates	%Sensitive										
		PG	FLU	ERY	DA	AMP	SXT	CIP	NIT	VA	TEC	LZD
Enterococcus	55			11%		87%			89%	98%	100%	100%
Candida	32											
Grp B Strep	7	100%		86%	100%	100%				100%		
S.aureus	2	0%	100%	50%	100%		100%	100%	100%	100%		
Total	**96**											

Blood Stream Infections.
Renal Transplant Unit PAH 2001-2012

Unit	Specific Acquisition	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013 to mid May	Total
renal transplant	inpatient healthcare associated	1	12	2	6	8	6	14	8	10	12	10	7	1	97
	non-inpatient healthcare associated		1		4	4	6	5	2	3	3	6	3		37
renal transplant Total		***1***	***13***	***2***	***10***	***12***	***12***	***19***	***10***	***13***	***15***	***16***	***10***	***1***	***134***

Blood Culture Isolates.
Renal Transplant Unit PAH 2008-Oct 2013

Organism	Number of isolates	% Pathogens	% Total Organisms
E.coli	27	40%	23%
S.aureus	12	18%	10%
Klebsiella	7	10%	6%
ESCAPPM	7	10%	6%
Pseudomonas	5	7%	4%
Proteus	2	3%	2%
Candida	2	3%	2%
Enterococcus	2	3%	2%
Other GNB	1	1%	1%
Cryptococcus	1	1%	1%
Haemophilus	1	1%	1%
S.pneumoniae	1	1%	1%
Pathogen total	**68**		**58%**
Contaminants	49		**42%**
Total organisms	**117**		

Blood Culture Isolates.
Renal Transplant Unit PAH 2008-Oct 2013

Pathogen	No. of Isolates	%Sensitive										
		AMP	AUG	CFZ	CRO	SXT	TMP	GEN	TOB	TAZ	CIP	MER
E.coli	27	33%	81%	81%	100%	67%	67%	100%		95% (18/19)	93%	100%
Klebsiella	7	0%	71%	86%	86%	57%	57%	86%		100% (6/6)	86%	100%
ESCAPPM	7	0%	0%	0%	100%	71%	67% (4/6)	100%		100% (6/6)	86%	100%
Pseudomonas	5							100%	100%	100% (2/2)	100%	83%
Proteus	2	100%	100%	100%	100%	100%	100%	100%		100%	100%	100%
Haemophilus	1	100%	100%		100%	100%						
Other	1	0%			0%	100%		0%			100%	100%
Total	**50**											

Pathogen	No. of Isolates	%Sensitive										
		PG	FLU	ERY	DA	AMP	GMS	SXT	CRO	VA	TEC	LZD
S.aureus	12	0%	75%	58%	75%			75%		100%		100%
Enterococcus	2			0%	0%	100%	0%			100%	100%	100%
S.pneumoniae	1	0%		100%					100%			
Candida	2											
Cryptococcus	1											
Total	**18**											

Multi-Resistant Organism Acquisition
PAH Renal Transplant Unit 2001-May 15 2013

Years	Clostridium difficile	K.pneumoniae (ESBL)	MRAB	Multiresistant MRSA	Non-multiresistant MRSA	UK EMRSA-15	VRE Van A	VRE Van B	Total
2001				14	1				15
2002		1		17		1		1	20
2003			1	6	3				10
2004		1		10	4				15
2005	2	1		20					23
2006	6			17					23
2007	1			20	1				22
2008	2	1		7				2	12
2009	1			23				9	33
2010	2	1		6				13	22
2011	2			4				10	16
2012	4	1		1				16	22
2013 to May 15	3	1			1		1	3	9

Infectious diseases and Transplantation

- PAH ID consult database (“ID Con-Man”)
  - Systematic collection of consult data since 2001
  - 11000+ entries, diagnoses limited to formal list
  - 512 renal transplant entries
    - >50 final diagnoses
    - 5 top diagnostic groups:
      - Pneumonia
      - Urosepsis
      - Skin/soft tissue infection
      - Osteomyelitis
      - Fever of unknown origin
    - Classic infections of immunocompromised a minority

- *Pneumocystis jirovecii*
- Multi-antibiotic resistant Gram negatives
- Bacterial and fungal Infection prevention initiatives
  - Prophylaxis

- *CMV, BKV, Hepatitis in a later presentation*

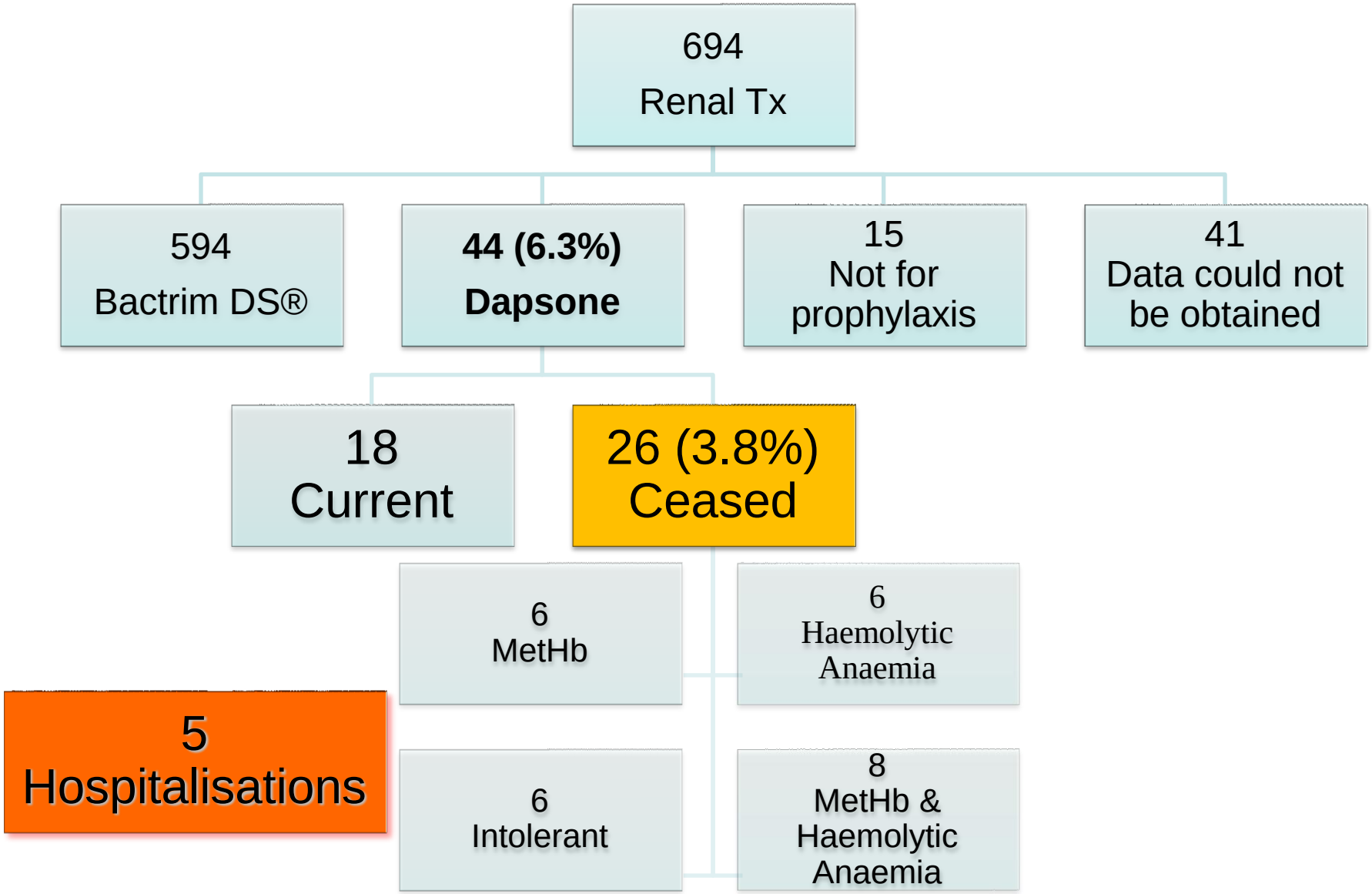
Pneumocystis jirovecii "PCP"

- A fungus that infects most humans, but immunosuppressed develop disease
- Worldwide increase in incidence since 2000, and not HIV related
- May be new strains circulating
- Outbreaks in Australia, mainly centred in renal transplant units
  - PAH 2011-12 14 cases 5 deaths, 5+ other cases outside renal unit, probably community acquired, all non HIV immunosuppressed
  - Westmead 14 proven cases, 3 likely 4 deaths
    - Typing showed likely to be clonal and new strain (S Chen, W Meyer)
  - Other units eg RPAH also involved
- Epidemiology suggested contact in clinic waiting rooms

Pneumocystis jirovecii

- Outbreaks include many >6 months post transplant
- Cotrimoxazole prophylaxis should be considered for all transplant patients
- When to cease?? Probable life long prophylaxis
  - Systematic ongoing surveillance required esp those not on prophylaxis
- Different regimens work,
  - 1 single strength Co-Tdaily (half DS)
- Alternatives for Co-T allergic
  - Desensitise
  - Dapsone 100 mg daily
  - Dapsone plus pyrimethamine plus leucovorin
  - Nebulised pentamidine
  - Atovaquone

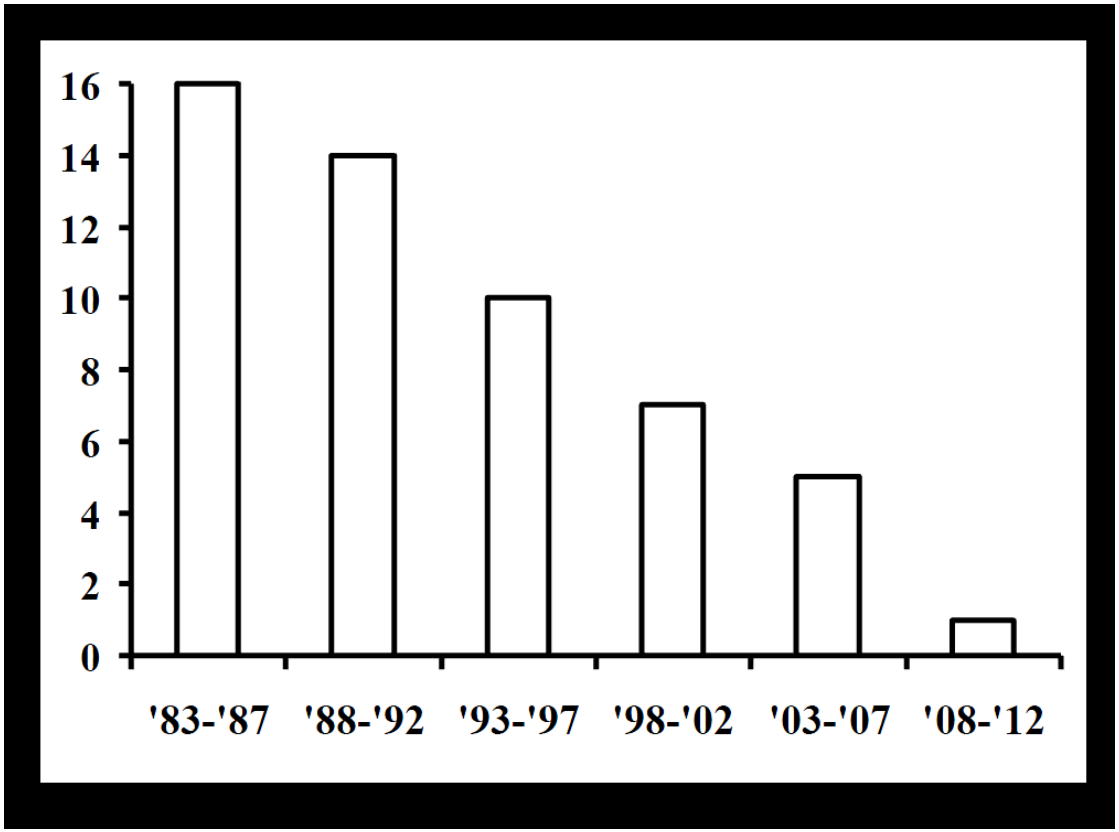
PAH PCP prophylaxis experience end 2012



Antibiotic resistance

The pipeline of new agents is drying up

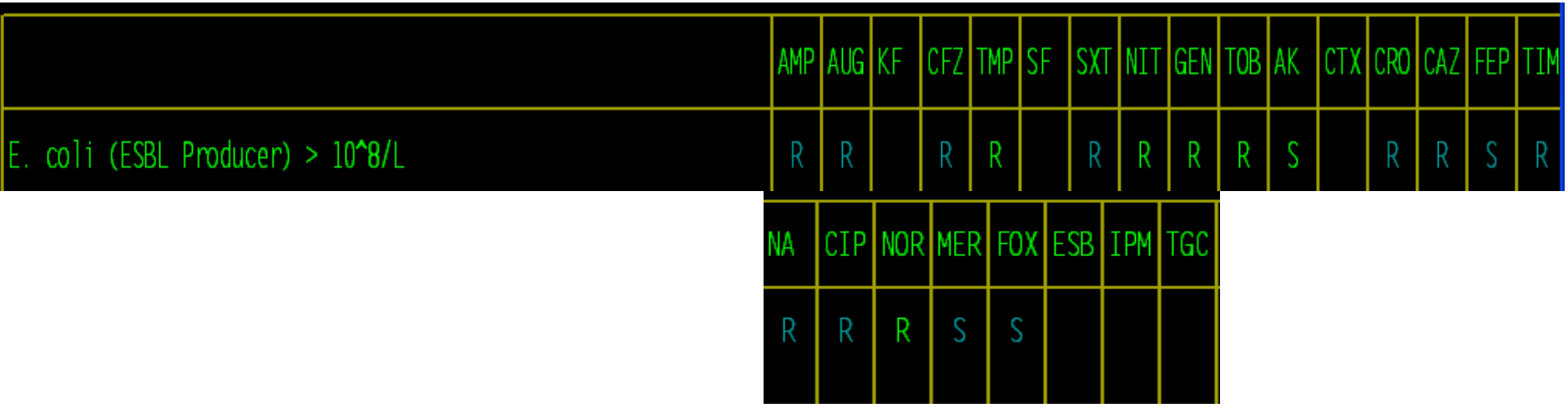
Total antibacterials approved for use by USA FDA



From IDSA Capitol Hill talk by Brad Spellberg May 11 2010.
www.idsociety.org/Content.aspx?id=4810

Extended Spectrum Beta-Lactamase producing (ESBL) E coli, Klebsiella, Proteus, Citrobacter, Enterobacter, Serratia

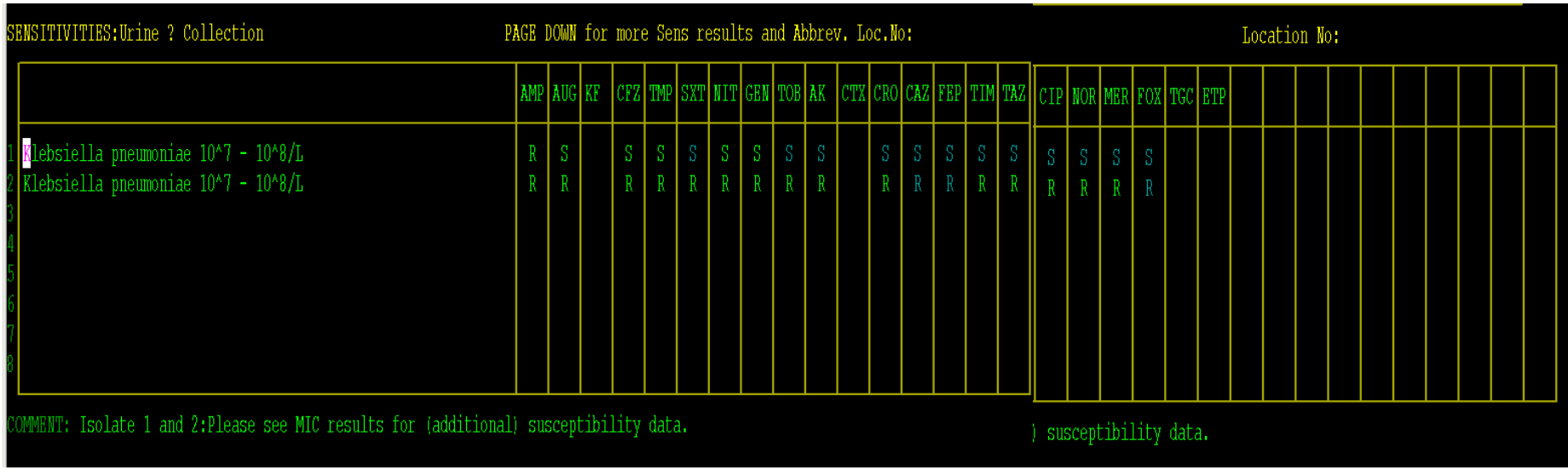
- Presenting as urosepsis from the community
- May be associated with long term care facilities
- Cross infection in hospital variable
- Returned travellers and medical tourists
- Post transplant urosepsis and surgical site infection



	AMP	AUG	KF	CFZ	TMP	SF	SXT	NIT	GEN	TOB	AK	CTX	CRO	CAZ	FEP	TIM
E. coli (ESBL Producer) > 10^8/L	R	R		R	R		R	R	R	R	S		R	R	S	R

NA	CIP	NOR	MER	FOX	ESB	IPM	TGC
R	R	R	S	S			

NDM positive K pneumoniae UTI. Colistin and tigecycline susceptible



SENSITIVITIES:Urine ? Collection PAGE DOWN for more Sens results and Abbrev. Loc.No: Location No:

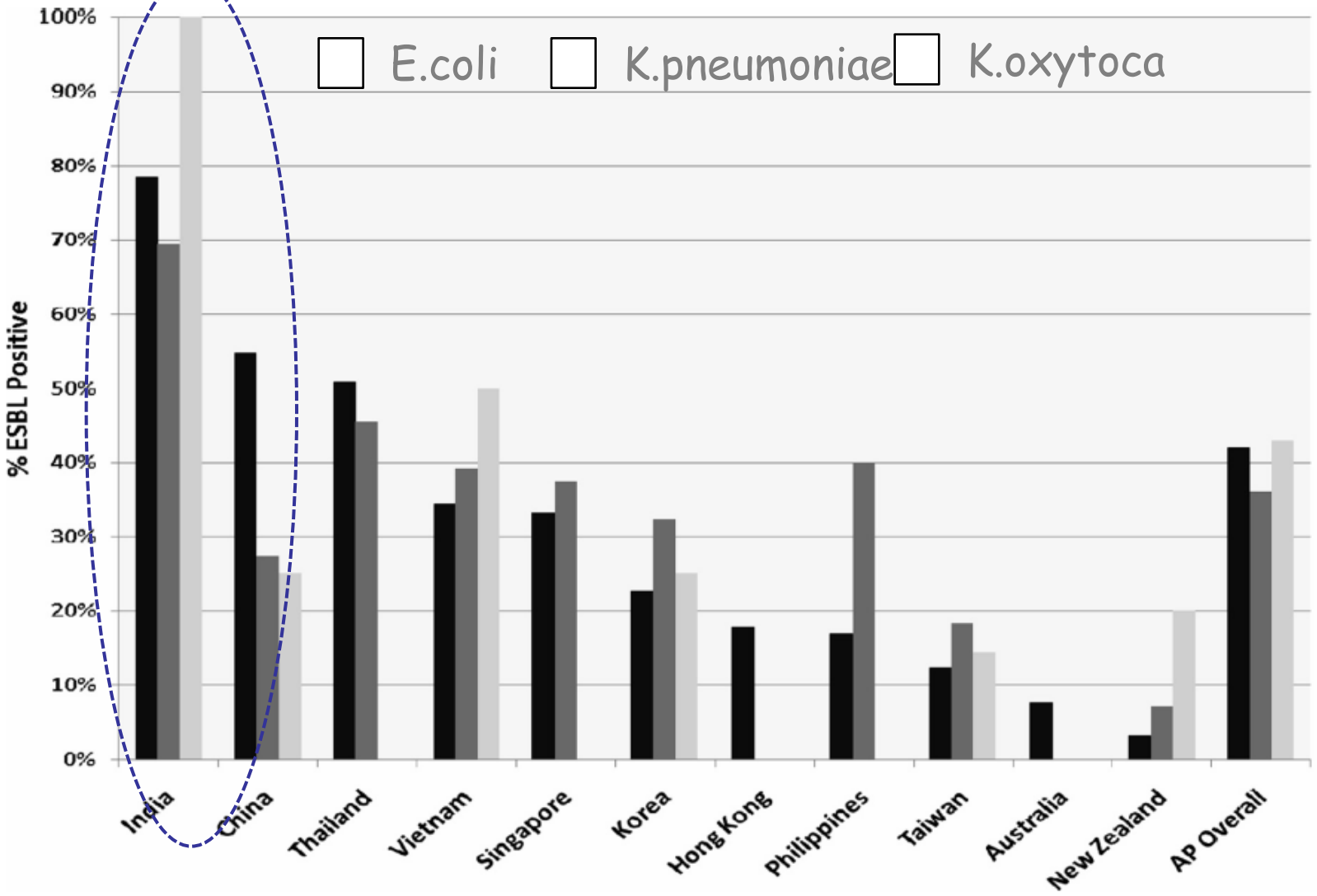
		AMP	AUG	KF	CFZ	TMP	SXT	NIT	GEN	TOB	AK	CTX	CRO	CAZ	FEP	TIM	TAZ	CIP	NOR	MER	FOX	TGC	ETP
1	Klebsiella pneumoniae 10^7 - 10^8/L	R	S		S	S	S	S	S	S	S		S	S	S	S	S	S	S	S	S		
2	Klebsiella pneumoniae 10^7 - 10^8/L	R	R		R	R	R	R	R	R	R		R	R	R	R	R	R	R	R	R		
3																							
4																							
5																							
6																							
7																							
8																							

COMMENT: Isolate 1 and 2:Please see MIC results for (additional) susceptibility data.

) susceptibility data.

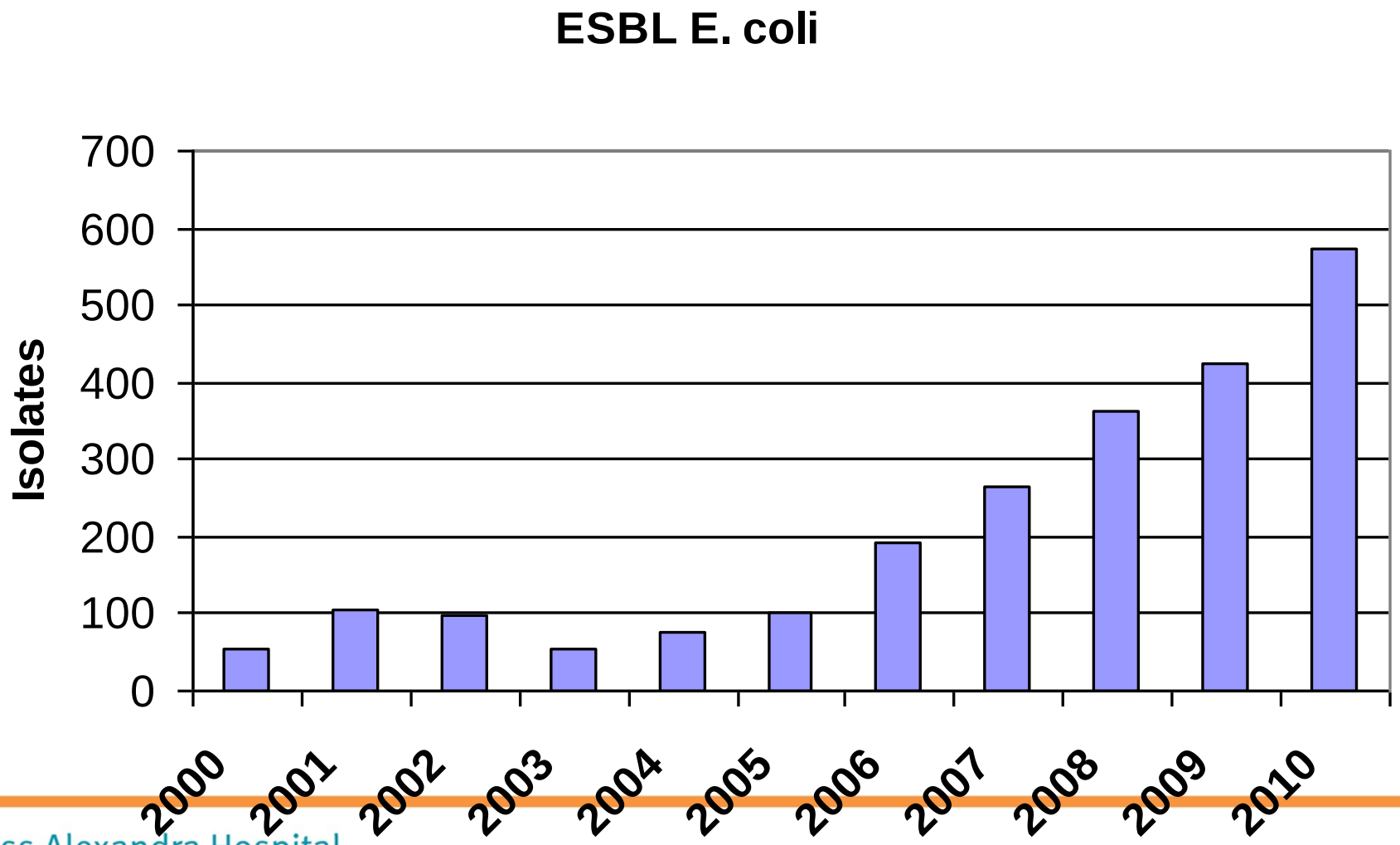
October 2013. Patient admitted for rehab. CVA in India and in Indian hospital. Discharged May 2013

Frequency distribution of ESBL-positive isolates in the Asia-Pacific (AP) region during SMART 2009



Hawser et al., AAC Aug 2009: 3280 - 3284

Example: all ESBL producing *E. coli* isolates over 10 years (Qld)



Travellers spreading resistant superbugs

Julie Robotham HEALTH EDITOR
September 16, 2010

OVERSEAS travel is emerging as an important factor behind the spread of antibiotic-resistant superbugs, as holidaymakers, particularly to India and other parts of Asia, become colonised with foodborne bacteria.

What about returned travellers ?

- Self collected rectal swabs pre/post travel
- ESBL multi resistant *E coli* acquired by 40%
- persist in follow up to 3/12;
- Most clear by 6/12

E.Coli resistance (n=99)

	Pre-travel	Post-travel
Aminoglycosides	7%	38%*
Ciprofloxacin	3%	32%*
3rd generation cephalosporins	1% (1 ESBL)	24%* (20 ESBL/4 AmpC)
Any combination	7%	47%*

Kennedy K. Eur J Clin Micro ID. *2010, 29:1501-1506*

Article Views
- Abstract
- Full Text
- Full Text (PDF)
- Supplementary Materials

Article Tools
- Save to My Folders
- Download Citation
- Alert Me When Article is Cited
- Post to CiteULike
- E-mail This Page
- Submit an E-Letter
- Rights & Permissions
- Commercial Reprints and E-Prints

Related Content

Similar Articles In:
- Science Translational Medicine

Search Google Scholar for:
- Articles by Snitkin, E. S.

Sci Transl Med 22 August 2012:
Vol. 4, Issue 148, p. 148ra116
Sci. Transl. Med. DOI: 10.1126/scitranslmed.3004129

RESEARCH ARTICLE

NOSOCOMIAL INFECTION

Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing

Evan S. Snitkin[1], Adrian M. Zelazny[2], Pamela J. Thomas[1], Frida Stock[2], NISC Comparative Sequencing Program[3], David K. Henderson[2], Tara N. Palmore[2,*] and Julia A. Segre[1,*]

+ Author Affiliations

* To whom correspondence should be addressed. E-mail: tpalmore@mail.nih.gov (T.N.P.); jsegre@nhgri.nih.gov (J.A.S.)

ABSTRACT

The Gram-negative bacteria *Klebsiella pneumoniae* is a major cause of nosocomial infections, primarily among immunocompromised patients. The emergence of strains resistant to carbapenems has left few treatment options, making infection containment critical. In 2011, the U.S. National Institutes of Health Clinical Center experienced an outbreak of carbapenem-resistant *K. pneumoniae* that affected 18 patients, 11 of whom died. Whole-genome sequencing was performed on *K. pneumoniae* isolates to gain insight into why the outbreak progressed despite early implementation of infection control procedures. Integrated genomic and epidemiological analysis traced the outbreak to three independent transmissions from a single patient who was discharged 3 weeks before the next case became clinically apparent. Additional genomic comparisons provided evidence for unexpected transmission routes, with subsequent mining of epidemiological data pointing to possible explanations for these transmissions. Our analysis demonstrates that integration of genomic and epidemiological data can yield actionable insights and facilitate the control of nosocomial transmission.

Citation: E. S. Snitkin, A. M. Zelazny, P. J. Thomas, F. Stock, N. C. Program, D. K. Henderson, T. N. Palmore, J. A. Segre, Tracking a Hospital Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* with Whole-Genome Sequencing. *Sci. Transl. Med.* **4**, 148ra116 (2012).

Princess

Treatment options for MRGN with carbapenem resistance

- Enterobacteriaceae:
  - Colistin (except Serratia and Proteus)
  - Tigecycline
  - Fosfomycin
- Acinetobacter:
  - Colistin
  - Tigecycline
- Pseudomonas
  - Colistin
  - Fosfomycin

Multi Resistant Gram Negatives in nephrology

- Outbreaks should be managed rapidly and thoroughly
- Next few years will determine whether they become more established in the community
- Prophylaxis protocols will need to be rethought
- Transplanting carriers?
- Pre transplant screening?
- New ways of managing transplant without antibiotics need to be investigated
- Cotrimoxazole prophylaxis may become ineffective for preventing urosepsis

Therapeutic Prescription in Transplantation*

- Treatment of Underlying Disease
- Prevention and Treatment of Graft Rejection
- Antimicrobial Strategy
  - Therapeutic
  - Prophylactic
  - Empiric
  - Pre-emptive

dePauw B, Rubin RH. Transplant Infect Dis 2007; 9:1-2

Prophylactic antimicrobials in renal transplantation

- Surgical prophylaxis
- Trimethoprim sulfamethoxazole
  - PCP prophylaxis
    - Effective against:
      - Nocardia
      - Listeria
      - Uropathogens
      - Some Staph aureus
      - melioidosis
- CMV: Valganciclovir
- Hepatitis B: Lamivudine
- *Mycobacterium tuberculosis*: isoniazid
- Antifungals: calcineurin antagonists active. ? contribution

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2008, p. 735–738 Vol. 52, No. 2
0066-4804/08/$08.00+0 doi:10.1128/AAC.00990-07

Calcineurin Inhibitor Agents Interact Synergistically with Antifungal Agents In Vitro against *Cryptococcus neoformans* Isolates: Correlation with Outcome in Solid Organ Transplant Recipients with Cryptococcosis▽

Dimitrios P. Kontoyiannis,[1]* Russell E. Lewis,[1] Barbara D. Alexander,[2] Olivier Lortholary,[3] Françoise Dromer,[4] Krishan L. Gupta,[5] George T. John,[6] Ramon del Busto,[7] Goran B. Klintmalm,[8] Jyoti Somani,[9] G. Marshall Lyon,[9] Kenneth Pursell,[10] Valentina Stosor,[11] Patricia Muñoz,[12] Ajit P. Limaye,[13] Andre C. Kalil,[14] Timothy L. Pruett,[15] Julia Garcia-Diaz,[16] Atul Humar,[17] Sally Houston,[18] Andrew A. House,[19] Dannah Wray,[20] Susan Orloff,[21] Lorraine A. Dowdy,[22] Robert A. Fisher,[23] Joseph Heitman,[3] Nathaniel D. Albert,[1] Marilyn M. Wagener,[24] and Nina Singh[24]*

M. D. Anderson Cancer Center, University of Texas, Houston, Texas[1]; Duke University Medical Center, Durham, North Carolina,[2] Institut Pasteur and Faculté de Médecine Paris Descartes, Hôpital Necker-Enfants malades, Paris, France[3]; Institut Pasteur, Paris, France[4]; Postgraduate Institute of Medical Education and Research, Chandigarh, India[5]; Christian Medical College Hospital, Vellore, India[6]; Henry Ford Hospital, Detroit, Michigan,[7] Baylor University Medical Center, Dallas, Texas[8]; Emory University, Atlanta, Georgia[9]; University of Chicago, Chicago, Illinois[10]; Northwestern University, Chicago, Illinois[11]; Hospital General Universitario Gregorio Marañón, Madrid, Spain[12]; University of Washington, Seattle, Washington[13]; University of Nebraska, Omaha, Nebraska[14]; University of Virginia, Charlottesville, Virginia[15]; Ochsner Clinic

Renal Transplant

Surgical Antibiotic Prophylaxis Guidelines

PRE-OPERATIVE CONSIDERATIONS

Drug administration

- Slow IV bolus – should be given ≤ 60 minutes before skin incision (ideally at 30 minutes). Administration after skin incision or > 60 minutes before incision reduces effectiveness
- IV infusion – should be timed to end ≤ 30 minutes before skin incision

Pre-existing infections (known or suspected) – if present, use appropriate treatment regimen instead of prophylactic regimen for procedure. Doses should be scheduled to allow for re-dosing just prior to skin incision.

PROPHYLAXIS REGIMEN

Procedures	First line regimen	Alternative (Penicillin hypersensitivity)
Renal Transplant	**Piperacillin / Tazobactam 4.5g IV** infused over 30 minutes before incision	**Vancomycin 1g IV** infused over 100 minutes before incision, (**1.5g IV** for patients > 80 kg infused over 150 minutes) plus **Aztreonam 2g IV** bolus over 5 minutes before incision
Removal of Tenckhoff	**Treat exit site infection if present according to culture results, otherwise no antibiotics required**	
Removal of Stent	**Treat UTI if urine cultures positive. Nil antibiotics required if urine cultures negative.**	

MRSA COLONISATION

Patients with a history of MRSA colonisation or infection

ADD

Vancomycin 1g IV infused over 100 minutes before incision (**1.5g IV** for patients > 80 kg infused over 150 minutes)

VRE COLONISATION

Patients with VRE colonisation or infection, consider adding

Teicoplanin 800mg IV (single dose only) (1200mg IV for patients > 100 kg) if

- Bowel is entered
- Prosthetic material placement
- Instrumentation of urinary tract and VRE present in urine

(Vancomycin is not required if concurrently MRSA colonised)

DURATION OF PROPHYLAXIS

All perioperative prophylaxis is a single dose at induction of anaesthesia. Treatment of active infection requires a significant treatment course of appropriate antibiotics.

Immunisation and Renal transplantation

- Childhood vaccines
  - MMR, Pertussis, Dipth, Tet, Rotavirus, HIB,
  - Hepatitis B and A
- Pneumococcal vaccine
- Meningococcal vaccine
- Influenza vaccine
- Varicella: Zostervax
- Reboost prior to transplant?
- New vaccines: Norovirus, C difficile within 10yrs

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Norovirus Vaccine against Experimental Human Norwalk Virus Illness

Robert L. Atmar, M.D., David I. Bernstein, M.D., Clayton D. Harro, M.D., Mohamed S. Al-Ibrahim, M.B., Ch.B., Wilbur H. Chen, M.D., Jennifer Ferreira, Sc.M., Mary K. Estes, Ph.D., David Y. Graham, M.D., Antone R. Opekun, P.A.-C., Charles Richardson, Ph.D., and Paul M. Mendelman, M.D.

ABSTRACT

BACKGROUND

Noroviruses cause epidemic and sporadic acute gastroenteritis. No vaccine is available to prevent norovirus illness or infection.

METHODS

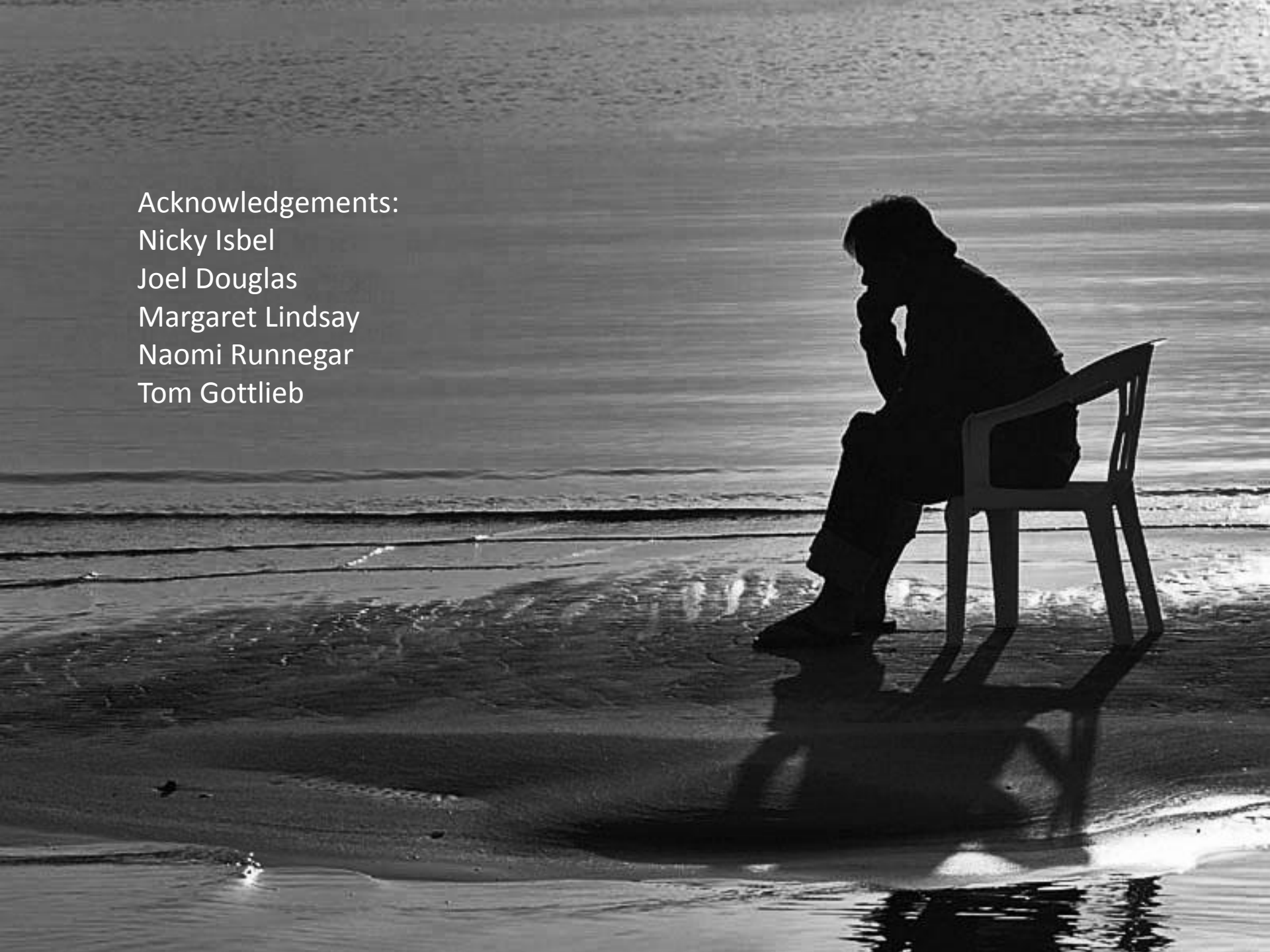
We conducted a randomized, double-blind, placebo-controlled, multicenter trial to assess the safety, immunogenicity, and efficacy of an investigational, intranasally delivered norovirus viruslike particle (VLP) vaccine (with chitosan and monophosphoryl lipid A as adjuvants) to prevent acute viral gastroenteritis after challenge with a homologous viral strain, Norwalk virus (genotype GI.1). Healthy adults 18 to 50 years of age received two doses of either vaccine or placebo and were subsequently inoculated with Norwalk virus and monitored for infection and gastroenteritis symptoms.

RESULTS

Ninety-eight persons were enrolled and randomly assigned to receive vaccine (50 participants) or placebo (48 participants), and 90 received both doses (47 participants in the vaccine group and 43 in the placebo group). The most commonly reported symptoms after vaccination were nasal stuffiness, nasal discharge, and sneezing. Adverse events occurred with similar frequency among vaccine and placebo recipients. A Norwalk virus–specific IgA seroresponse (defined as an increase by a factor of 4 in serum antibody levels) was detected in 70% of vaccine recipients. Seventy-seven of 84 par-

Transplant Infectious Diseases

- In urban centres, transplant outcomes are generally good and infectious complications are uncommon and generally easily managed
- Multi resistant Gram negatives are the most immediate and obvious new challenge over next 10yrs
- Clinicians currently coping but using drugs of last resort
- No new antimicrobial agents on immediate horizon
- Other diseases likely to emerge without warning eg BKV
- MDR/XDR tuberculosis in high risk recipients is on the horizon
- Consideration should be given to systematically collecting infection related morbidity data, so that decisions on prophylaxis can be taken on the basis of good data



Acknowledgements:
Nicky Isbel
Joel Douglas
Margaret Lindsay
Naomi Runnegar
Tom Gottlieb