Infectious Complications of Transplantation

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OSPEDALE PEDIATRICO

Infection is the most common cause of death following renal transplantation

- Mortality (3 years post transplant follow up):
  - in living donor transplant: 260/5819: (4.5%)
  - deceased donor transplant: 331/5298 (6.3%)
- Infections: 168/591 (28.4%)
- Cardiopulmonary: 86 (14.6%)
- Malignancy: 68/591 (11.5%)
- dialysis-related complications: 18 (3%)

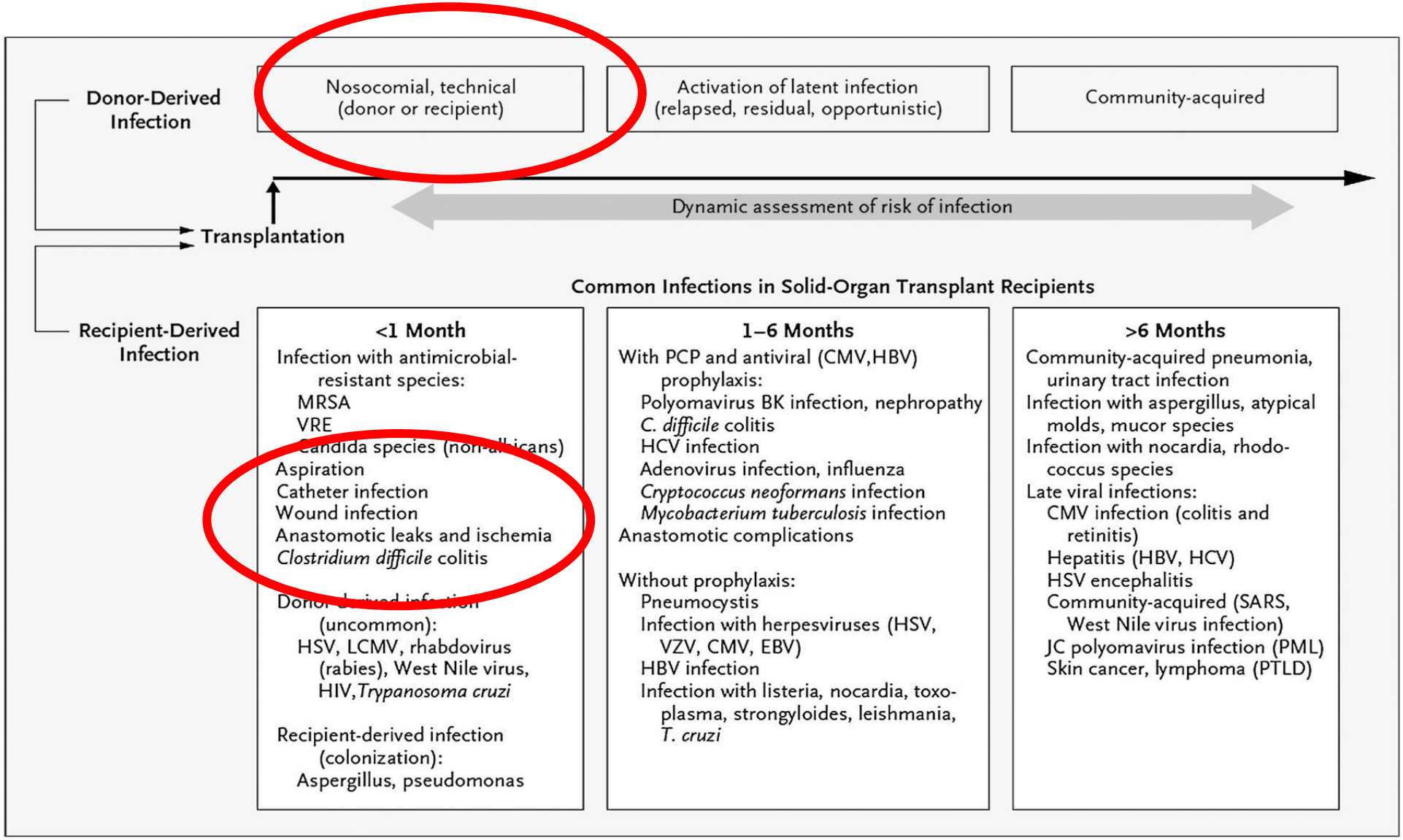
NAPRTCS 2014 Annual Transplant Report

	Total			Living Donor			Deceased Donor		
	N	%	Func graft	N	%	Func graft	N	%	Func graft
All deceased patients	591	100.0	285	260	100.0	131	331	100.0	154
Cause of Death									
Infection,Viral	47	8.0	25	26	10.0	14	21	6.3	11
Infection,Bacterial	75	12.7	38	35	13.5	16	40	12.1	22
Infection, Not Specified	46	7.8	15	23	8.8	8	23	6.9	7
Cancer/malignancy	68	11.5	49	38	14.6	28	30	9.1	21
Cardiopulmonary	86	14.6	39	31	11.9	15	55	16.6	24
Hemorrhage	33	5.6	12	9	3.5	2	24	7.3	10
Recurrence	10	1.7	1	4	1.5	1	6	1.8	0
Dialysis-related Complications	18	3.0	0	8	3.1	0	10	3.0	0
Other	149	25.2	76	64	24.6	35	85	25.7	41
Unknown	59	10.0	30	22	8.5	12	37	11.2	18

- Not a “pediatric” problem, but children are naive to many common infections
- Age 9-12 years - EBV seropositive 60%

» *J Clin Virol 37 (2006) 118–123*

Timeline of common infections in transplant recipients.



Karuthu S , and Blumberg E A CJASN 2012;7:2058-2070

Pretransplant factors—donors

expected and possibly anticipated:

- CMV, EBV, BK
- *bacterial*
- (*Toxoplasma)*

rare - unexpected

- *Mycobacterium tuberculosis,*
- *Histoplasma* spp.,
- West Nile virus (WNV),
- hepatitis B (HBV) and C viruses (HCV)
- human immunodeficiency virus (HIV)

Am J Transpl 2013; 13: 3–8

Pretransplant factors—recipients

- ***age:*** community-acquired viruses, pre transplant status (EBV, CMV, …)
- Primary renal disease: posterior urethra valves, neurogenic bladder

Am J Transpl 2013; 13: 3–8

risk factor for infection after transplantation

- Accidental contamination (perfusion fluid culture)
- indwelling cannulas
- central venous catheters is associated with bloodstream infections;
- urethral catheters (vesicoureteral reflux)

Early infections (0–30 days after transplant)

- usually associated with the presence of preexisting conditions or complications of surgery.
- Bacteria and yeast are the most frequent pathogens recovered
- Superficial and deep surgical site infections are among the most common
- pneumonia
- Viral infections
- Nosocomial respiratory viruses

Intermediate period (1-6 months)

- typical time of onset of infections attributable to latent pathogens transmitted from donor organs and blood products and those reactivated within the recipient
- CMV, EBV
- Pneumocystis jiroveci

Late infections

- infection risks vary with immunosuppression and exposures
- EBV
- Community-acquired infections

Bacterial UTI

- Bacterial UTI is the most frequent infectious complication in kidney transplant recipients, occurring in up to 25% of patients during the first year after transplant .

Am J Transpl 2015; 15: 3024–3040

UTI

- The most common pathogens of UTI after kidney transplantation are E Coli, Klebsiella spp, Enterococcus spp and P. aeruginosa.
- The main risk factors for UTI are: age, female sex, and the need for immediate post-transplant dialysis

Am J Transpl 2015; 15: 3024–3040

UTI

- a significant association between UTI and impaired allograft function has not been confirmed
- may be due to non sophisticated methods to measure renal function

Am J Transpl 2015; 15: 3024–3040

UTI - asymptomatic bacteriuria

- asymptomatic bacteriuria is generally associated with similar outcomes in terms of kidney function
- systematic treatment may increase the rate of MDR organisms .
- Please note: randomized controlled trials to assess the efficacy of therapy for asymptomatic bacteriuria to improve long-term kidney function are currently lacking.

Am J Transpl 2015; 15: 3024–3040

BK polyomavirus infection

- BKV belongs to the polyomavirus family highly prevalent (>85%) in the general population.
- discovered in 1971 as a cause of allograft loss in kidney transplant recipients
- the actual impact of BKV nephropathy on allograft function and survival was recognized during the 1990s with the advent of more potent immunosuppressive regimens

Am J Transpl 2015; 15: 3024–3040

Polyomavirus-associated nephropathy

- 0.7% at 6 months post-transplantation, 2.18% at 1 year, 3.45% at 2 years and 6.6% at 5 years.
- graft loss due to BKV was 7.5% (70/938) in 2009 and 5.7% (36/632) in 2010.

Nat. Rev. Nephrol. 8, 390–402 (2012);

diagnosis

- Decoy cells: low positive predictive value (very cheap)
- quantitative PCR (Q-PCR) analysis in:
  - Urine: positive predictive value for PVAN of 20–30%, (similar to that of decoy cell)
  - Plasma: cut-off values between 3.0 × 103 and 1.0 × 104.5 copies per ml
- PVAN requires a histological diagnosis with viral cytopathic changes in tubular epithelial cells, inflammatory cell infiltrates and a positive immunostaining

Nat. Rev. Nephrol. 8, 390–402 (2012);

Proposed monitoring scheme

- Monthly BKV screening using plasma nucleic acid testing is advocated in the first 3–6 months,
- then every 3 months until 2 years after transplantation
- any unexplained decline in renal function or treatment for acute rejection should prompt additional testing

Nat. Rev. Nephrol. 8, 390–402 (2012);

Proposed management

- Pre-emptive reduction of immunosuppressive therapy for BKV viremia (sequential/simultaneous lowering of antimetabolite doses by 50% and doses of calcineurin inhibitors and proliferation signal inhibitors by 30–50%) results in viral clearance in 85–95% of cases

Nat. Rev. Nephrol. 8, 390–402 (2012);

Immunization

- While every effort should be made to vaccinate prior to transplantation, inactivated vaccines are generally safe after solid organ transplantation
- In general live vaccines are not administered after transplantation.
- Therefore, when possible it is recommended to administer live vaccines such as measles, mumps, rubella, Varicella vaccine prior to transplantation

Am J Transpl 2013; 13: 311–317

Clin J Am Soc Nephrol 7: 2058–2070, December, 2012

Table 1: Recommendations for immunization of pediatric patients

Vaccine	Inactivated/ live attentuated (I/LA)	Recommended before transplant[1]	Recommended after transplant	Monitor vaccine titers	Quality evidence
Influenza (17–21)	I	Yes	Yes	No	II-1
	LA	See text	No	No	III
Hepatitis B[2] (22–28)	I	Yes	Yes	Yes	II-1
Hepatitis A[3] (29,30)	I	Yes	Yes	Yes (see footnote)	II-1
Pertussis	I	Yes	Yes	No	III
Diphtheria (31–34)	I	Yes	Yes	No	II
Tetanus (31–34)	I	Yes	Yes	Yes	II-1
Inactivated Polio vaccine (31)	I	Yes	Yes	No	II-2
H. influenzae[4] (35)	I	Yes	Yes	Yes	II-1
S. pneumoniae[5] (conjugate vaccine) (1,13–15,36,37)	I	Yes	Yes	Yes	II-1
S. pneumoniae[5] (polysaccharide vaccine) (1,13–15,36,37)	I	Yes	Yes	Yes	II-1
N. meningitidis[6] (1,38)(MCV4)	I	Yes	Yes	No	III
Human papillomavirus (HPV)[7].	I	Yes	Yes	No	III
Rabies[8]	I	Yes	Yes	Yes (see footnote)	III
Varicella (live-attenuated)[9] (39–42)	LA	Yes	No	Yes	II-1
Rotavirus	LA	Yes	No	No	III
Measles[9] (43–46)	LA	Yes	No	Yes	II-1
Mumps[9] (43,46)	LA	Yes	No	Yes	II-1
Rubella[9] (32,43,46)	LA	Yes	No	Yes	II-1
BCG[10]	LA	Yes	No	No	III
Smallpox[11] (47)	LA	No	No	No	III
Anthrax	I	No	No	No	III

Table 3
Vaccination after kidney and liver transplant

Vaccines Safe to Give After Transplant	Vaccines Contraindicated After Transplant
Hepatitis A	Anthrax
HBV	BCG (Bacillus Calmette–Guérin)
Human papilloma virus	Influenza (intranasal)
Inactivated polio	MMR
Influenza (inactivated)	Smallpox
Neisseria meningitidis	Varicella zoster
Pertussis (Tdap)	
Rabies	
S pneumoniae both PCV-13 (pneumococcal conjugate vaccine) and PPSV-23 (pneumococcal polysaccharide vaccine)	
Tetanus	

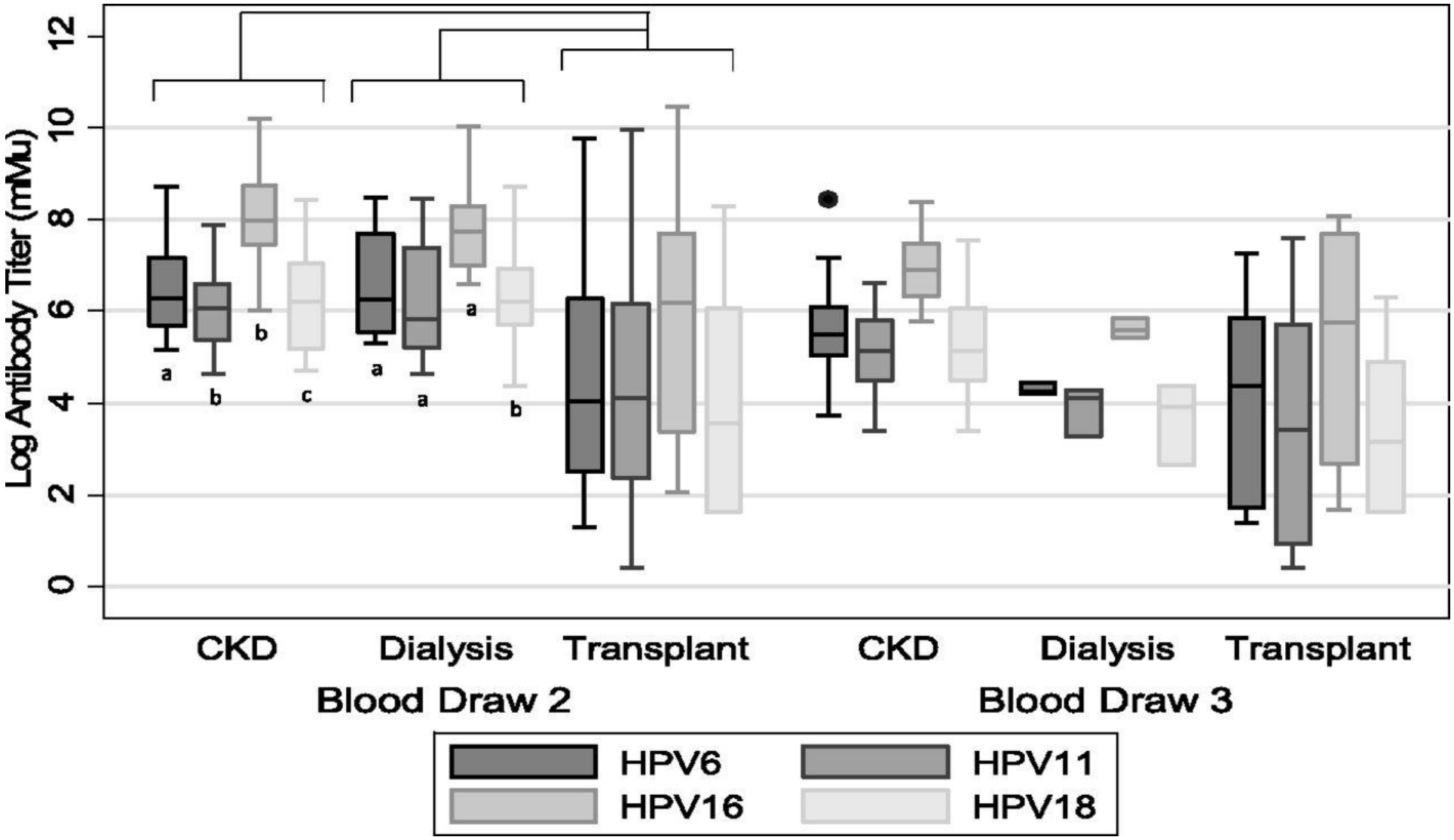
Med Clin North Am. 2016 May;100:587-98.

Specific issues: HPV

- cohort study including 57 girls (age 9-21 years)
  - CKD (n=25)
  - dialysis (n=9)
  - transplantated (n=23)
- quadrivalent HPV vaccine (genotypes 6, 11, 16, 8)
- Antibody levels were measured before vaccine, <12 months after vaccine and ≥12 months after vaccine

Clin J Am Soc Nephrol. 2016 May 6;11(5):776-84

Boxplot of logarithmically transformed IgG antibody titers by CKD status at blood draws 2 and 3.

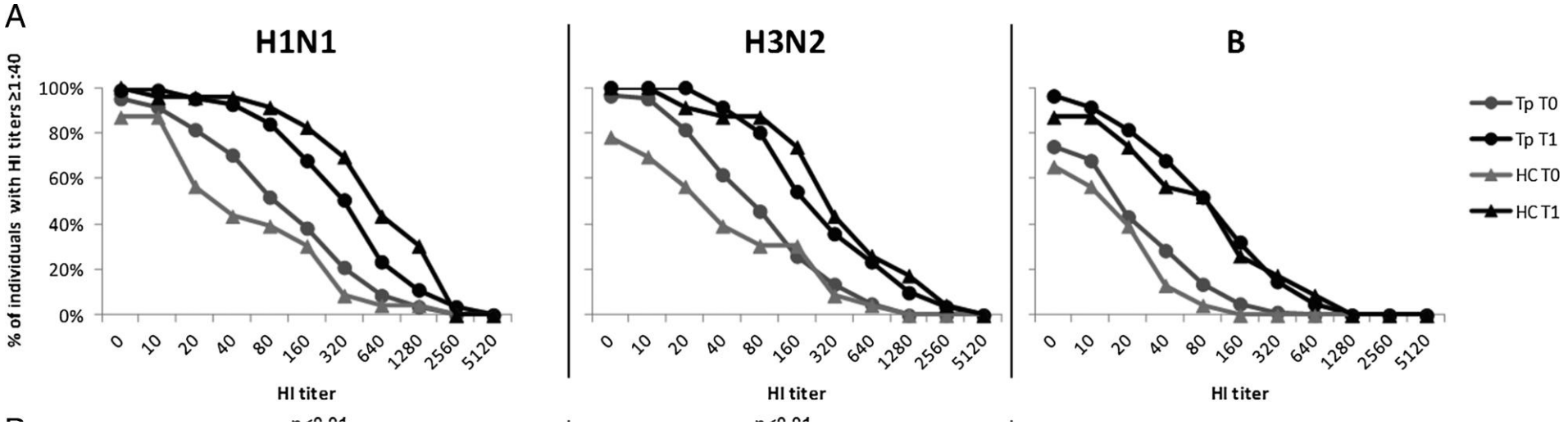


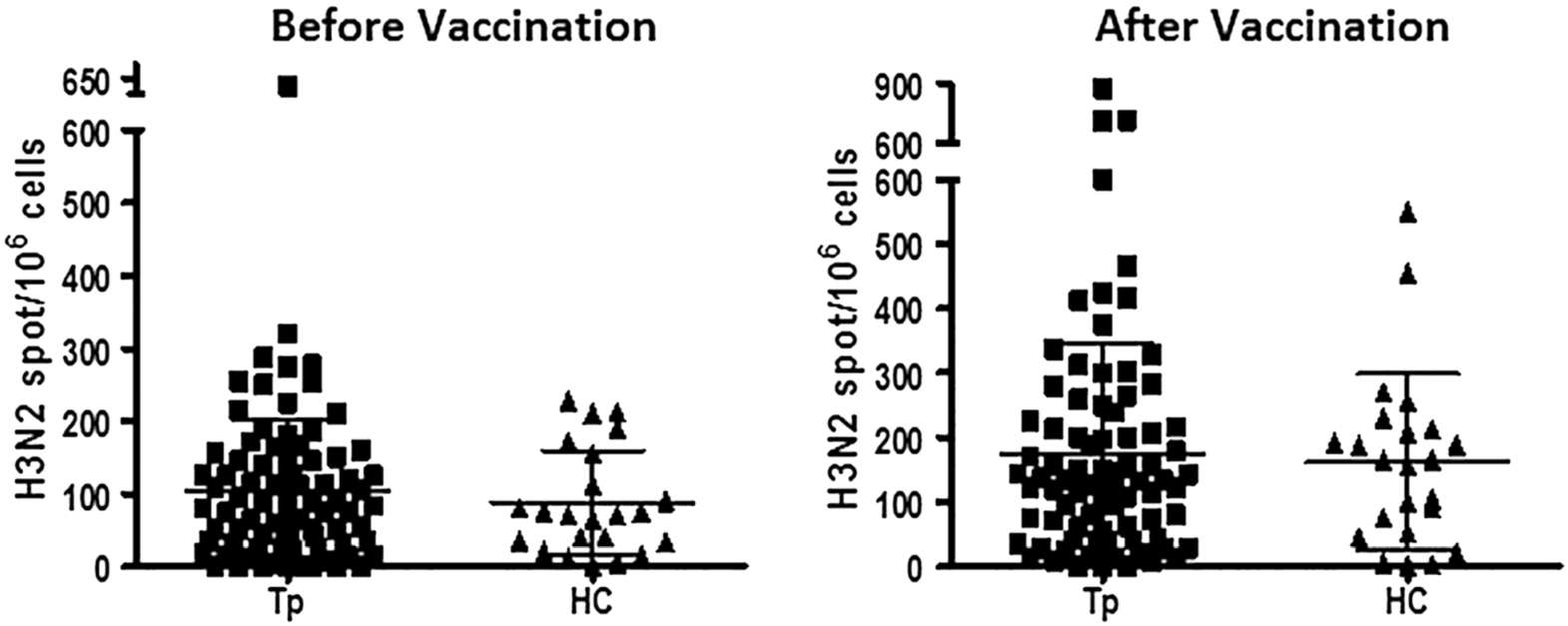
Delphine R. Nelson et al. CJASN 2016;11:776-784

Specific issues: flu

- influenza vaccine is recommended annually,
- vaccine given in the first 6 months post-transplant is poorly immunogenic but is unlikely to pose an increased safety risk.
- Vaccination (3) 6 months after transplant could be considered if still within the seasonal time period for influenza.
- What about health care workers?

Am J Transpl 2013; 13: 311–317


A
H1N1
H3N2
B
% of individuals with HI titers ≥1:40
100%
80%
60%
40%
20%
0%
0
10
20
40
80
160
320
640
1280
2560
5120
HI titer
Tp T0
Tp T1
HC T0
HC T1


Before Vaccination
After Vaccination
H3N2 spot/10^6 cells
650
600
500
400
300
200
100
0
900
Tp
HC
D
Tp group
HC group

question

- How much would you wait before testing immune response after vaccination?

answer

- A minimum of 4 weeks should elapse between vaccine administration and evaluation for seroconversion based on protective titers established in the literature.

Am J Transpl 2013; 13: 311–317

PROPHYLAXIS

Table 2
Prophylaxis after kidney and liver transplant

Prophylaxis Regimen	Patient Population That Receives It	Prophylaxis Directed Toward
TMP-SMX/dapsone/ atovaquone	Everyone	PJP Nocardia with TMP-SMX as well
Nystatin	Everyone	Candida
Valganciclovir	Seropositive CMV recipients Seronegative CMV recipients that receive a CMV+ organ	CMV, HSV
Valacyclovir/acyclovir	Seronegative CMV recipients that receive a CMV− organ	HSV
Entecavir/tenofovir	Recipients with a positive HBV core Ab Recipients of an organ from an HBV core Ab donor	HBV

?

Med Clin North Am. 2016 May;100(3):587-98.

CMV strategies: prophylaxis vs preemptive treatment

- (Universal) **prophylaxis** is the administration of antiviral drug to all “at-risk” patients for a defined period after SOT.
- **Preemptive** therapy is the administration of antiviral drug only to asymptomatic patients with evidence of early CMV replication in order to prevent CMV disease.

Am J Transpl 2013; 13: 93–106

CMV- prophylaxis

Organ	Risk category	Recommendation/options (see Table 2 for dose and text for special pediatric issues)	Evidence
Kidney	D+/R–	*Antiviral prophylaxis* is preferred	I
		Drugs: valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir	
		Duration: 6 months	
		Preemptive therapy is an option (see Figure 1).	I
		Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg [1]p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	
	R+	*Antiviral prophylaxis*	I
		Drugs: Valganciclovir, oral ganciclovir, intravenous ganciclovir or valacyclovir	
		Duration: 3 months	
		Preemptive therapy (see Figure 1).	I
		Weekly CMV PCR or pp65 antigenemia for 12 weeks after transplantation, and if a positive CMV threshold is reached, treat with (1) valganciclovir 900-mg[1] p.o. BID, or (2) IV ganciclovir 5-mg/kg IV every 12 h until negative test	

Am J Transpl 2013; 13: 93–106

CMV- prophylaxis

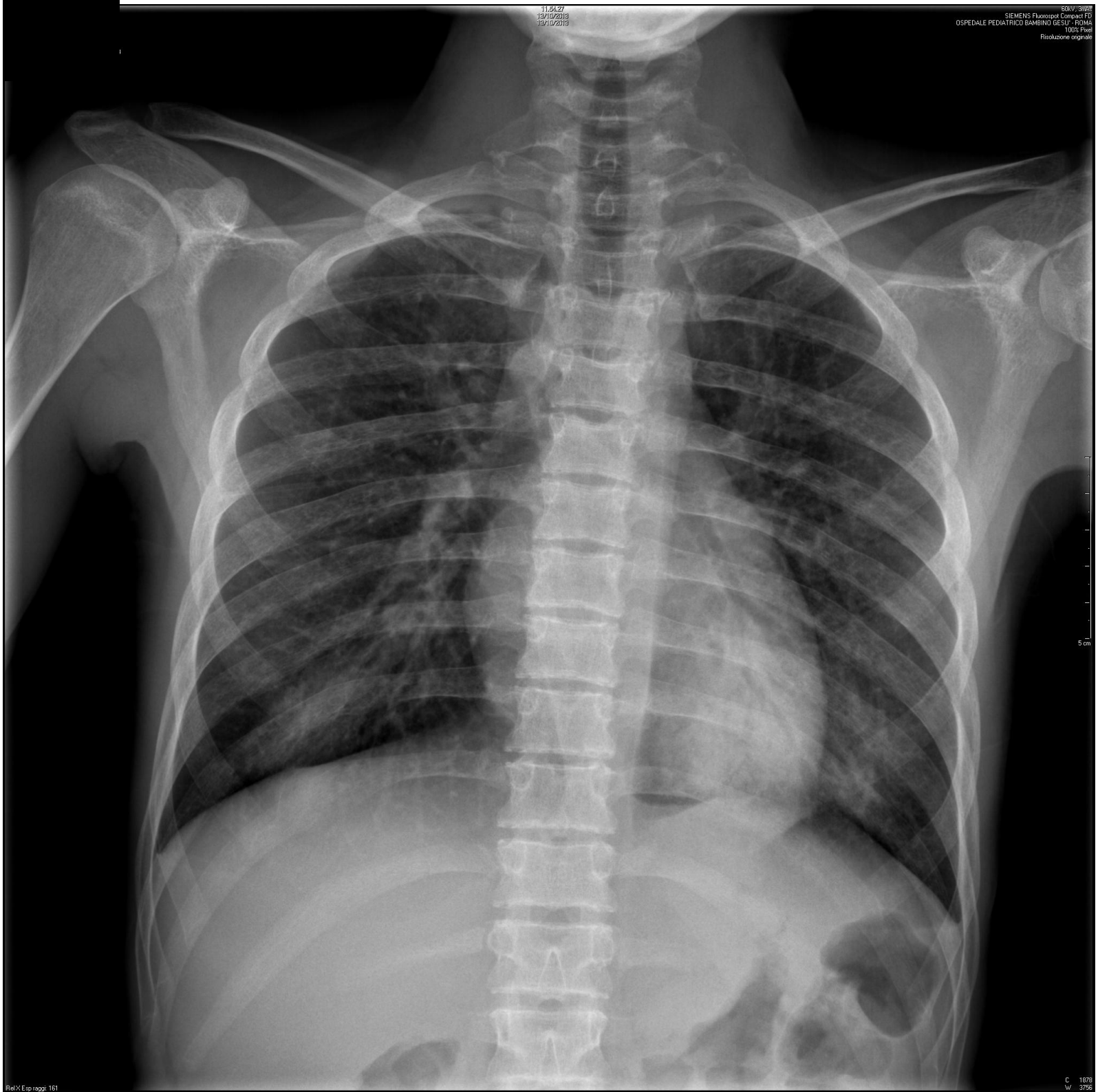
	Prophylaxis	Preemptive therapy
Efficacy	Yes: large randomized trials	Yes: smaller trials; fewer D+/R–
Ease	Relatively easy to coordinate	More difficult to coordinate Viral load thresholds not standardized
Late-onset CMV disease	Occurs commonly in CMV D+/R– transplant recipients	Occurs much less commonly
Cost	Higher drug costs	Higher laboratory costs
Toxicity	Greater drug toxicity (myelosuppression)	Potential for less drug toxicity with shorter courses of antivirals
Indirect effects (graft loss, mortality and opportunistic infections)	Positive impact based on meta-analyses and limited comparative trials	Very limited data that preemptive therapy affects indirect effects
Drug resistance	Yes	Yes

Am J Transpl 2013; 13: 93–106

Always look for an Early and “aggressive” diagnosis

Clinical case

- Male, 19
- Renal transplant at the age of 11
- Patients in poor general condition
- Fever and cough, dyspnoea
- O2 saturation 92% then 86%
- Temperature 38° C
- Physical examination: Basal crackles in the left lung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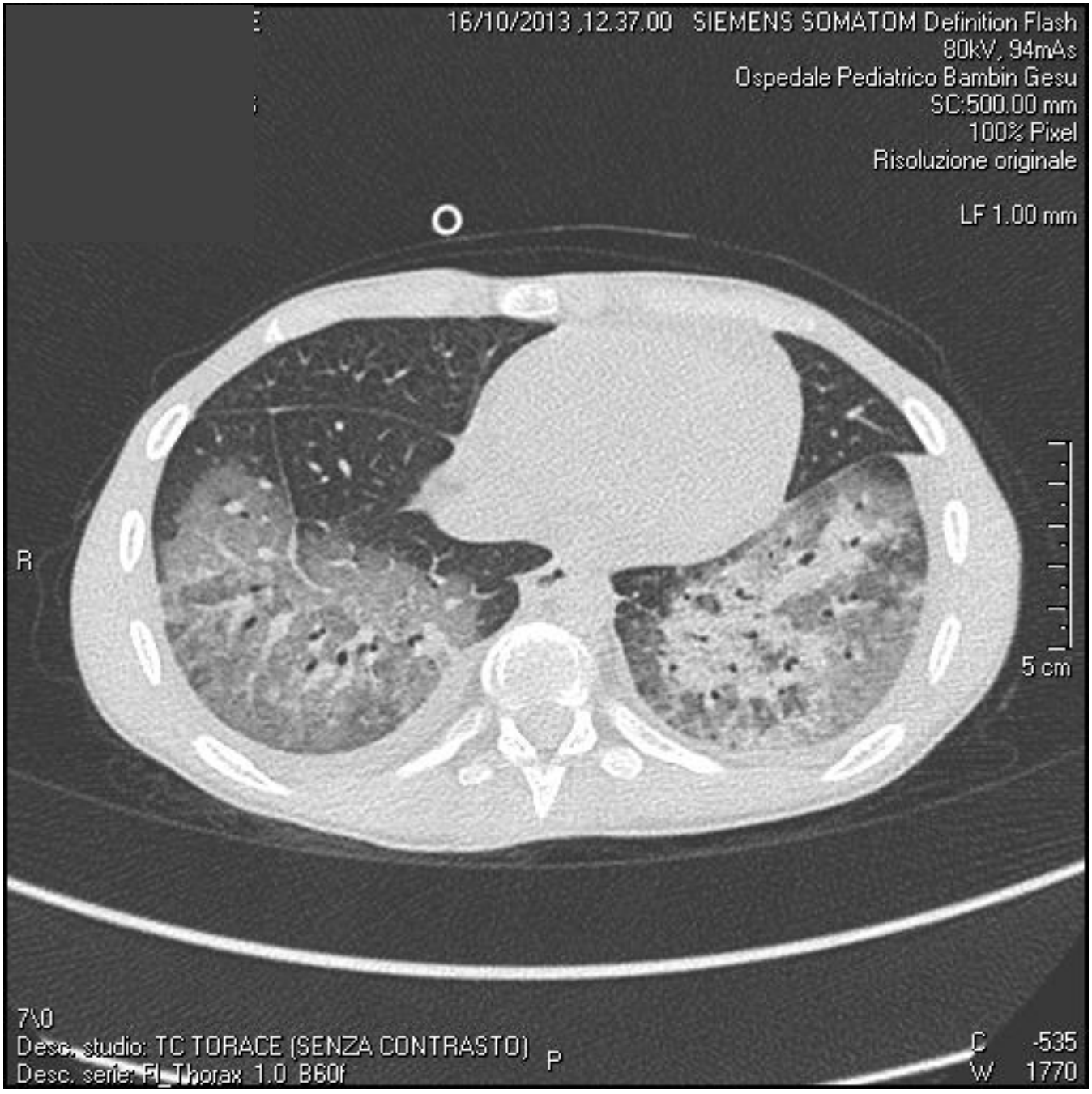
C 1878
W 3756

- Starts empirical treatment with Teicoplanin and ciprofloxacin
- No response
- Worsening of general conditions
- What would you do?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Bronchoalveolar lavage

- Positive cultura for: Leptotrichia
- anaerobic, gram-negative rod bacteria
- it is a constituent of normal oral flora

Respiratory disease

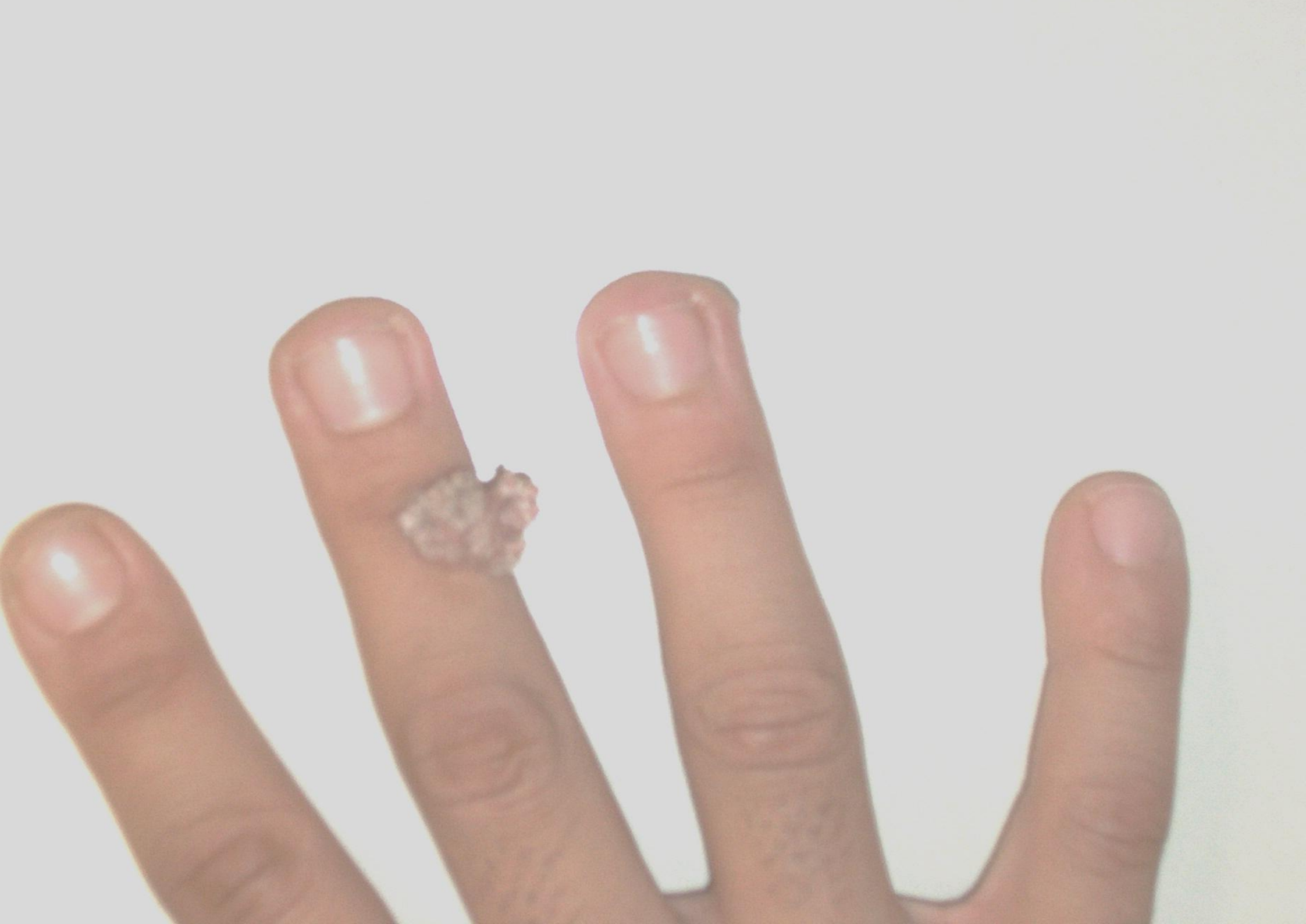
- Chest X ray
- Computerized tomography for interstitial disease
- Sputum and/or tracheobronchial aspirate
- bronchoalveolar lavage

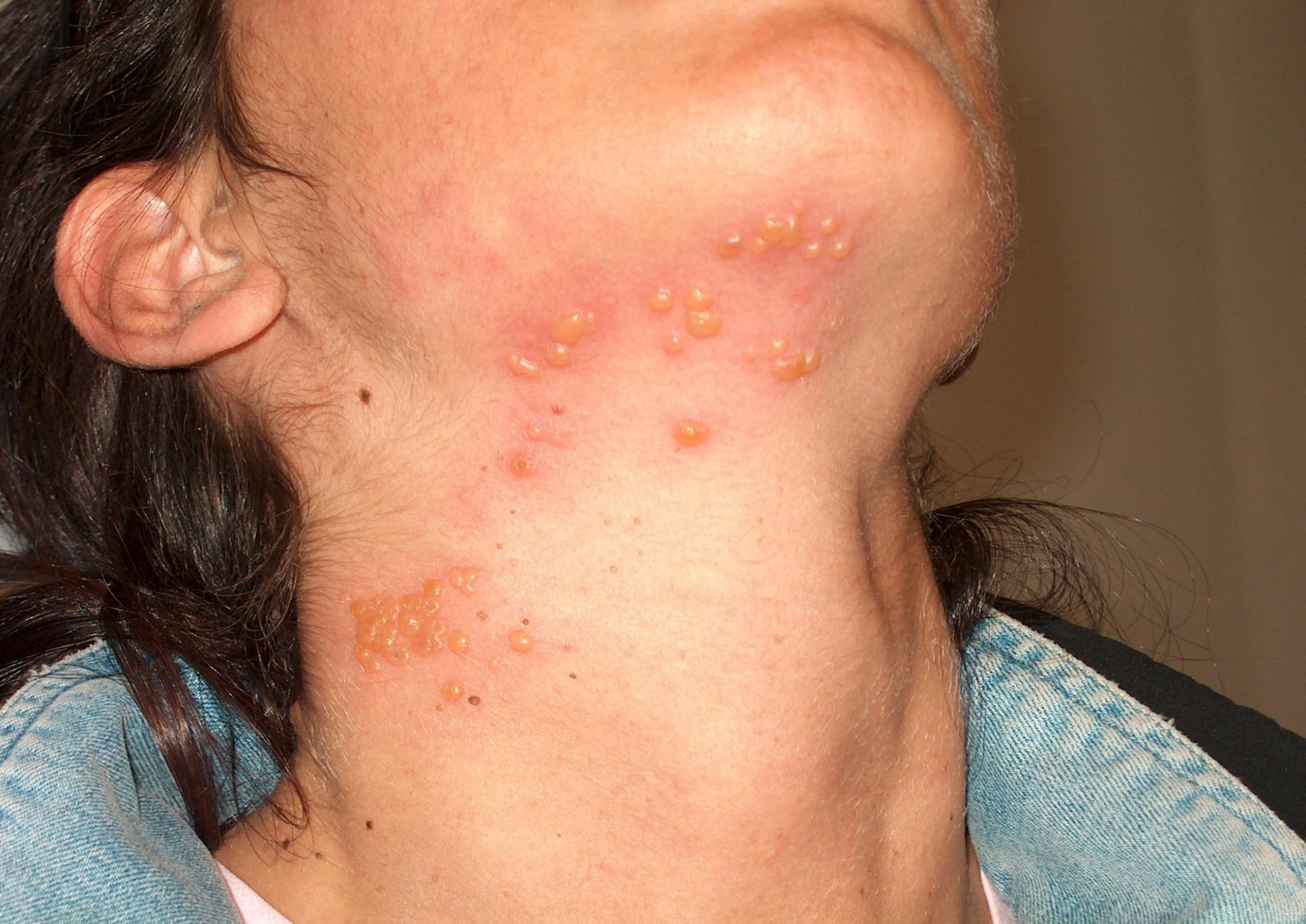
Gastrointestinal disease

- Stool Cultures for all germs (Salmonella, clostridium difficile, campylobacter, yersinia, candida)
- Search for fecal antigens (Rotavirus, Adenovirus, Giardia)
- PCR on stools for CMV
- If diagnosis is lacking: endoscopy
  - CMV lesions?
  - tuberculosis granulomatosis? (differential diagnosi with Chrohn disease!)

Think to “specific” diseases

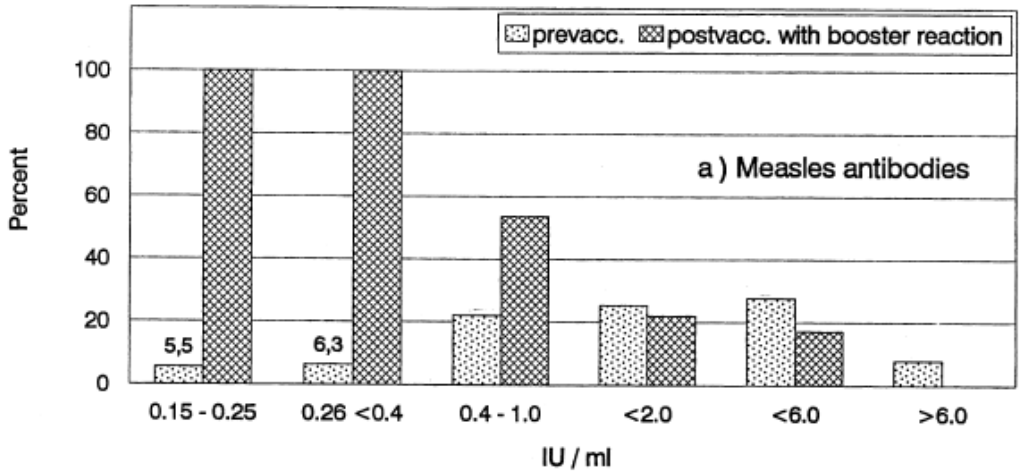
- Tubercolosis
- FLU (H1N1)
- ……

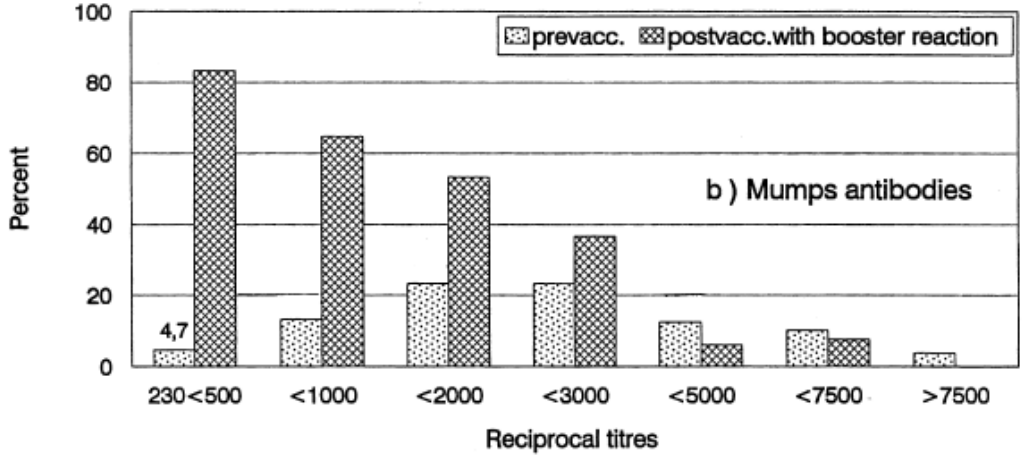


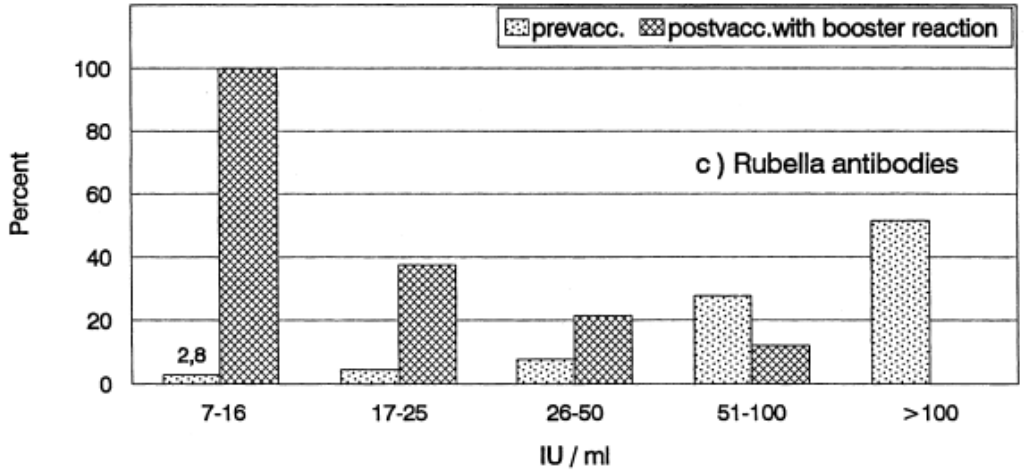


conclusions

- In spite of all our diagnostic facilities and antimicrobial agents, infections are still an important cause of mortality in renal transplanted children
- Prevention by means of immunization and prophylaxis is a very useful means to reduce mortality
- In case of any infection all efforts must be done to achieve a precise diagnosis in order to start an etiological treatment







Vaccine 18 (2000) 1382±1392