Centre des Grands Brûlés
Bruxelles

Problématique du Sepsis et des Infections à *Pseudomonas aeruginosa* dans un Centre de Brûlés

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Séminaire de Pathologie Infectieuse

UCL - 26 Avr 2007

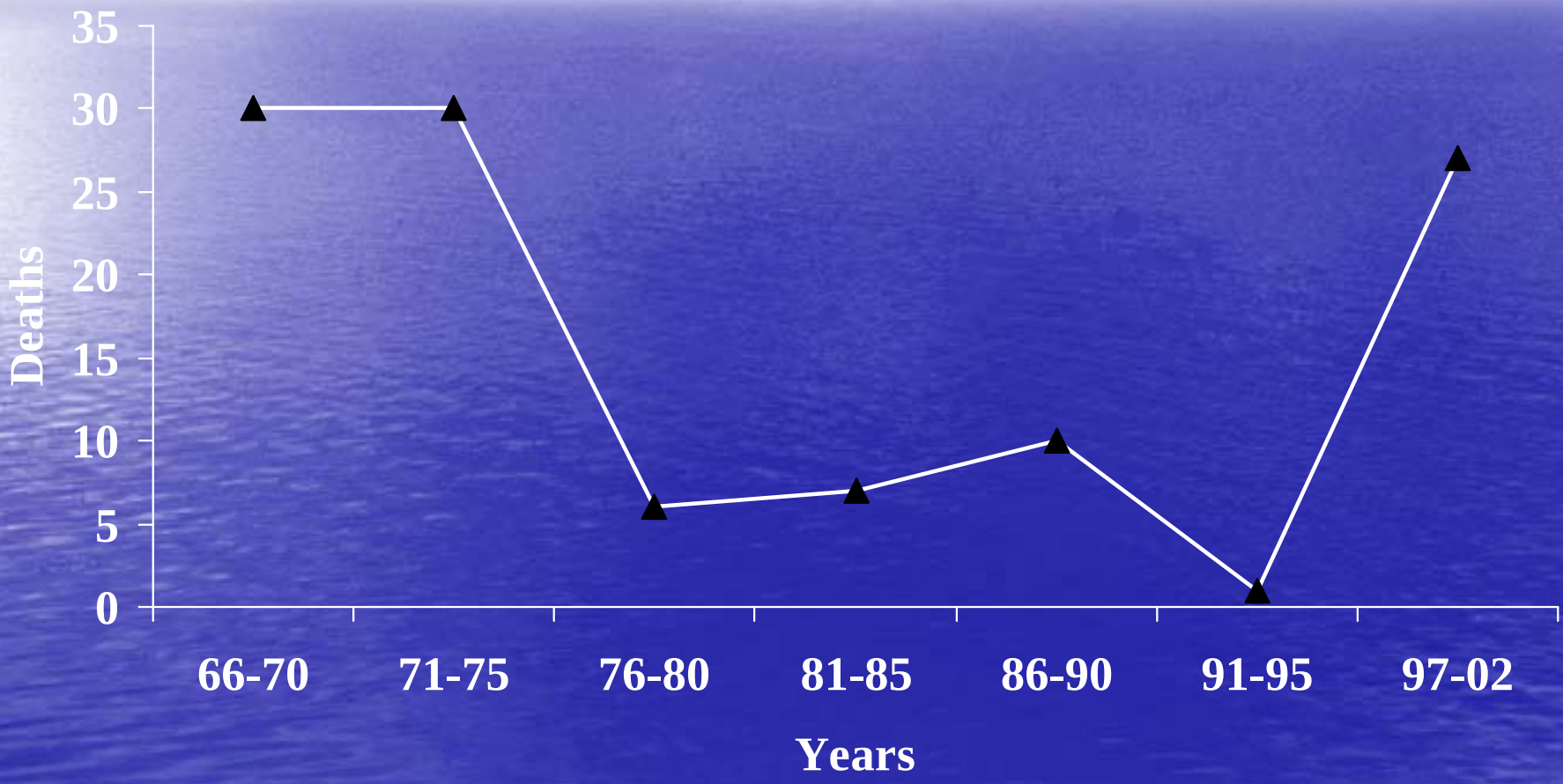
Decreased Mortality From Major Thermal Injury Has Been Due To Advances In:

- Resuscitation
- Control of Infection
- Support of the Hypermetabolic Response To Trauma
- Early Closure of the Burn Wound

Burn Mortality
(TBSA associated with LD50)

	Age Groups (years)			
	0-14	15-44	45-64	>65
Bull & Fisher (1942-52) 2807 Patients	49 n = 1366	46 n = 967	27 n = 330	10 n = 144
Bull 1967-70 1917 Patients	64 n = 962	56 n = 565	40 n = 246	17 n = 144
Curreri & Abston 1975-79 1508 Patients	77 n = 803	63 n = 413	38 n = 178	23 n = 114
SBI/UTMB 1980-89 2164 Patients	98 n = 1524	70 n = 450	46 n = 127	19 n = 63
SBI/UTMB 1989-2005 Patients 1722	98 n=1083	82 n=420	78 n=152	35 n=67

Deaths from Sepsis



Invasive Burn Wound Infections 1991-2004

Admissions:			**3,876**
Patients with Invasive Wound Infections			
Bacterial:			
Gram negative bacilli:	**20**		
Gram positive cocci:	**5**	**25**	
Fungal:			**90**
Aspergillus sp.:	**47**		
Mucor sp.:	**16**	**65**	
Candida sp.:	**2**		
Incidence			**2.3%**
Mortality			**55/90 (61%)**

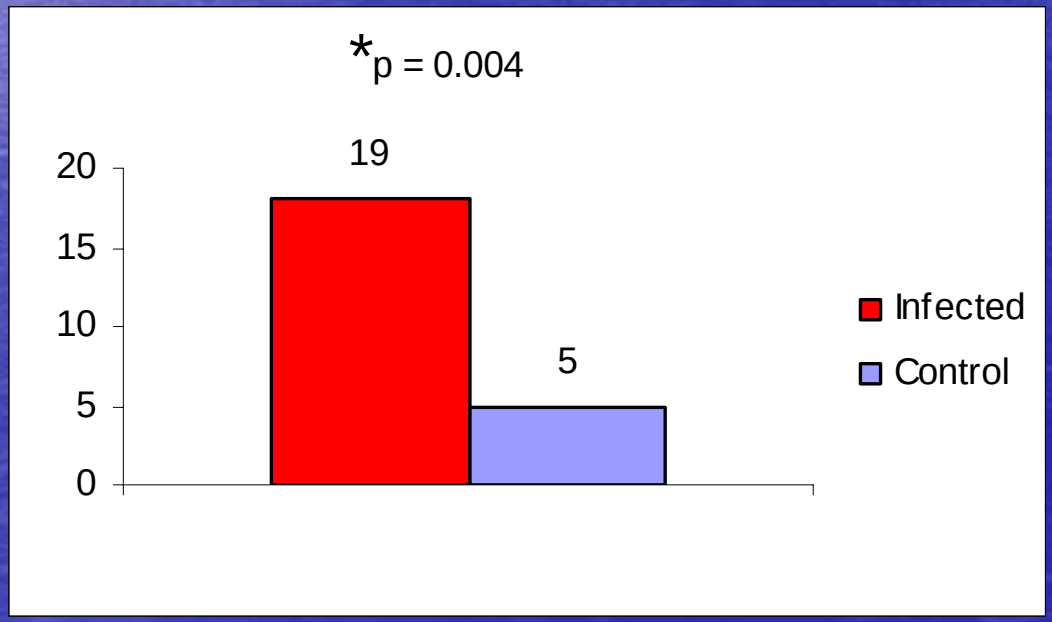
Increased Deaths from Sepsis Due to Antibiotic Resistant Organisms 1997-2002

Organism	# Deaths	Mean % Burn	Mean LOS (days)	Antibiotic Treatment
Fusarium	7	72%	28	Amphotericin
Acinetobacter	14	73%	29	Colistin
Vancomycin Resistant Enterococcus and Pan Resistant Pseudomonas	6	76%	37	

Fusarium: 7 deaths out of 8 patients admitted from mass disaster.

Mortality associated with Fungal Infection in Burns

- **30% of Burn Patients Become Colonized With Candida Sp. At Some Time During Their Acute Hospital Stay.**

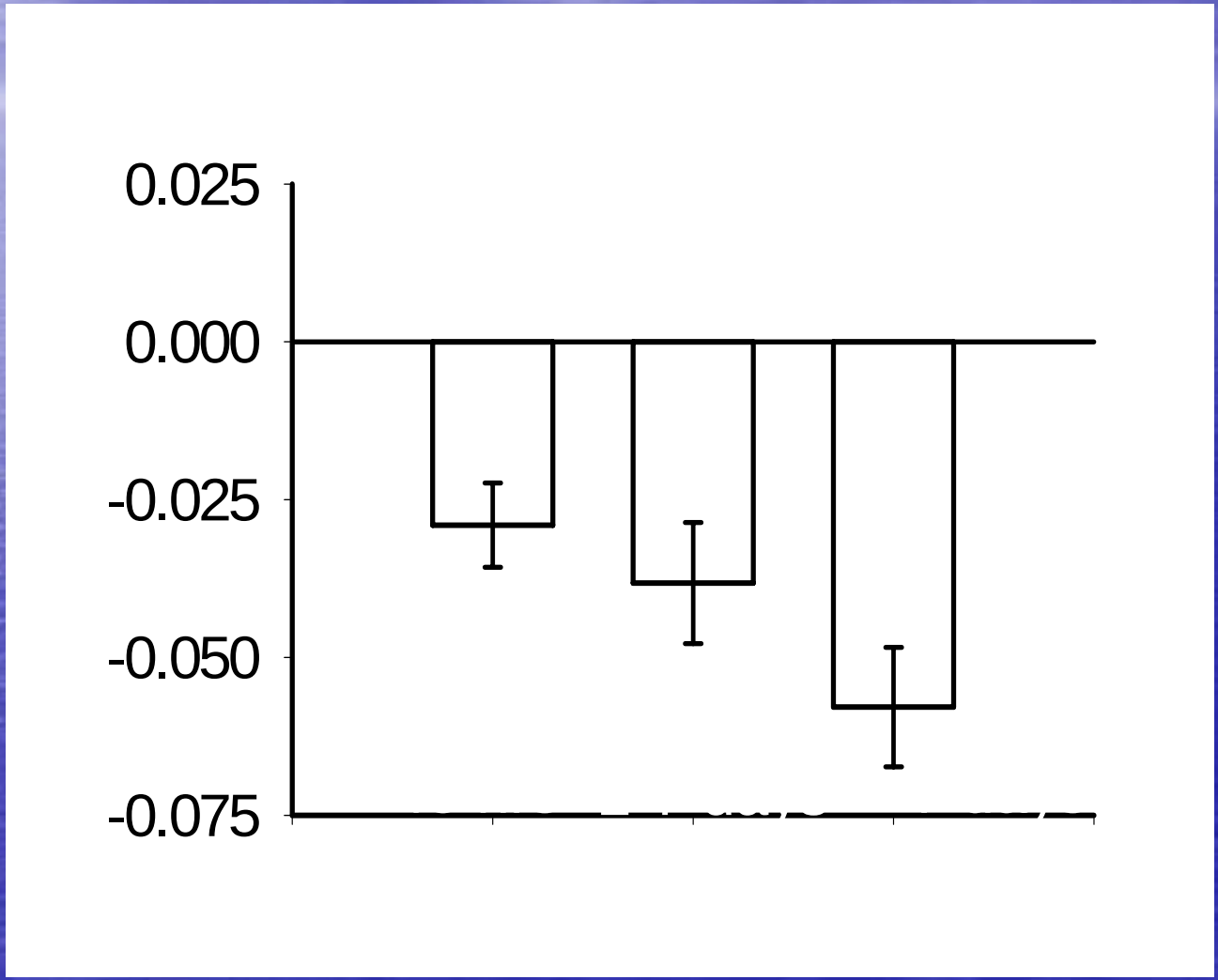


Decreased Mortality From Major Thermal Injury Has Been Due To Advances In:

- Resuscitation
- **Control of Infection**
- **Support of the Hypermetabolic Response**
- **Early Closure of the Burn Wound**

The Three Last are Related

Effect of Delay to Excision and Grafting on Protein Catabolism



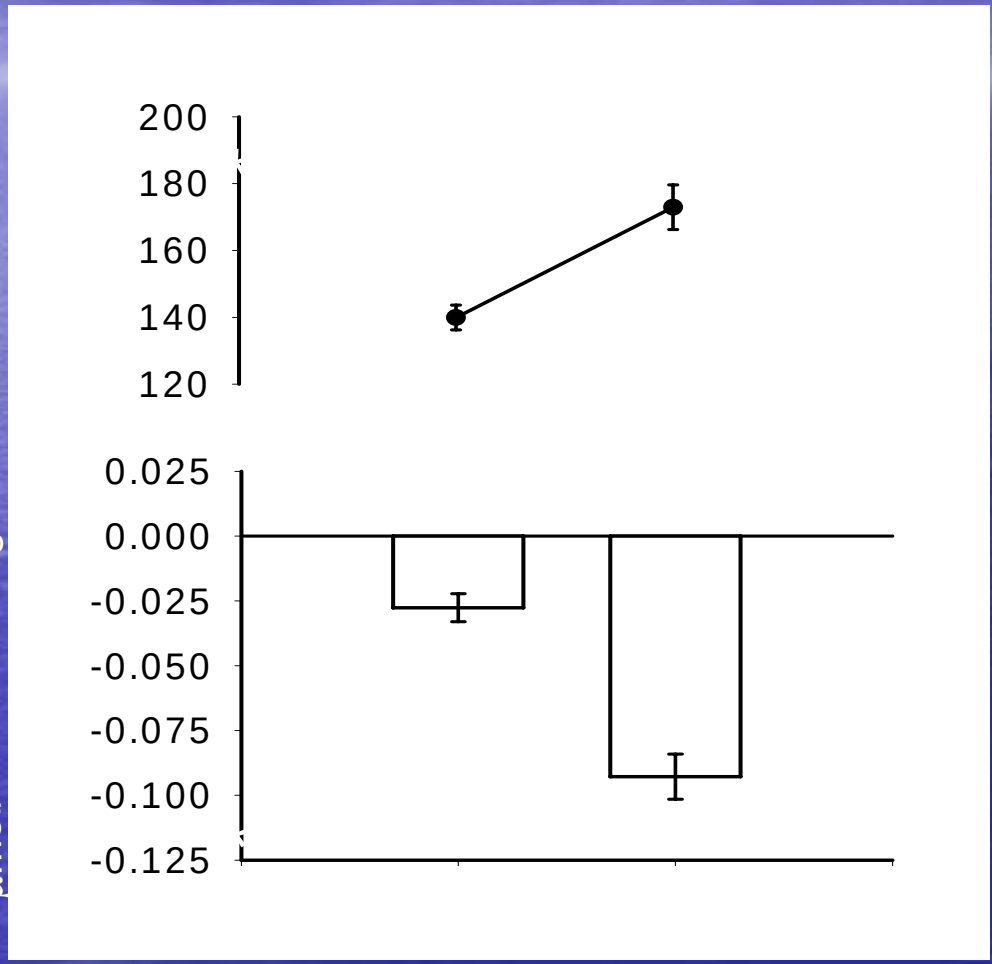
Hart et al. Determinants of skeletal muscle catabolism after severe burn. Ann. Surg. 233(4):455-465;2000.

Critically ill patients with sepsis showed:

- increases in metabolic rate
- loss of body protein associated with loss of skeletal hence respiratory muscle
- impaired immune response
- poor wound healing

Voerman et al

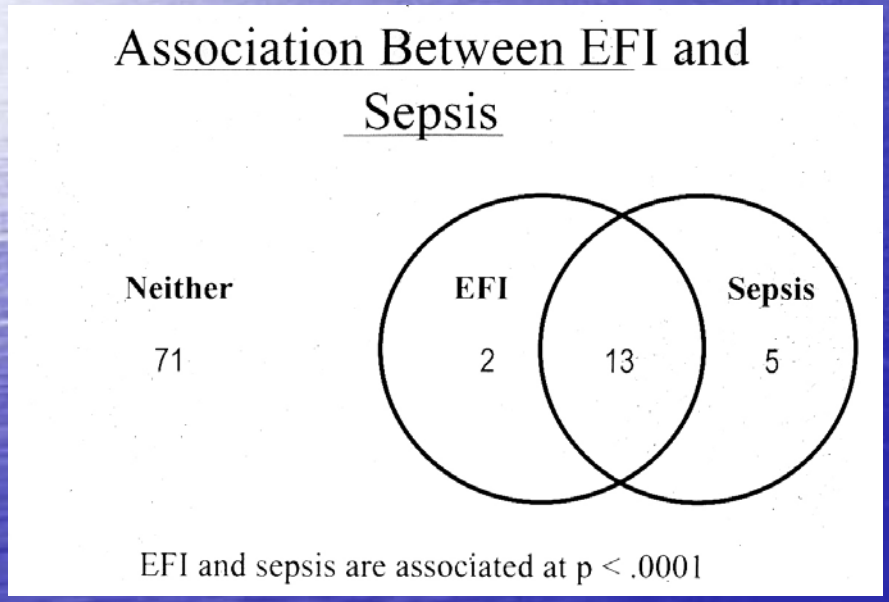
Effect of Burn Sepsis on Metabolic Rate and Protein Catabolism

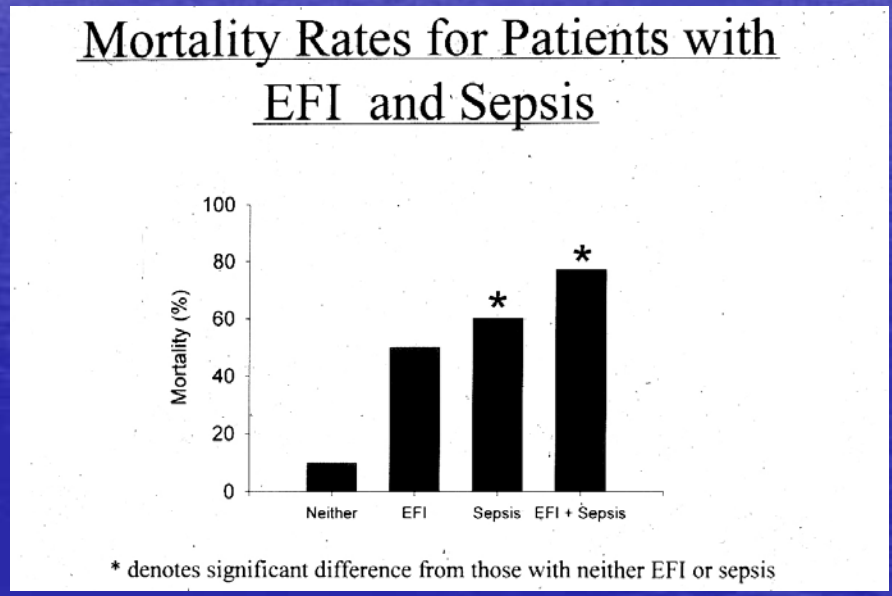


*p<0.0001

Hart DW, Wolf SE, Mlcak R, Chinkes DL, Ramxy PI, Obeng MK, Wolfe RR, Herndon DN. Persistence of muscle catabolism after severe burn. Surgery 2000; 128(2): 312-319.

Enteral Feeding Intolerance and Sepsis





Decreased Mesenteric Blood Flow

Decreased Gut Immune Function

Decreased Gut Mucosal Integrity

Decreased Ability to Prevent Bacterial Exodus from Lumen

Increase in Mucosal Permeability

Bacterial Translocation From The GI Tract

Complications of Catabolism

- **Consequences associated with erosion of body mass[1]**

% Lost	*Altered Physiology*	*% Mortality*
– 10 %	Impaired immune function	10 %
– 20 %	Decreased wound healing	30 %
– 30 %	Pneumonia, pressure sores	50 %
– 40 %	Death (pneumonia)	100 %

[1]Chang, DeSanti, Demling. *SHOCK*. 1998

Scoring & Definitions should be Specific for Burns

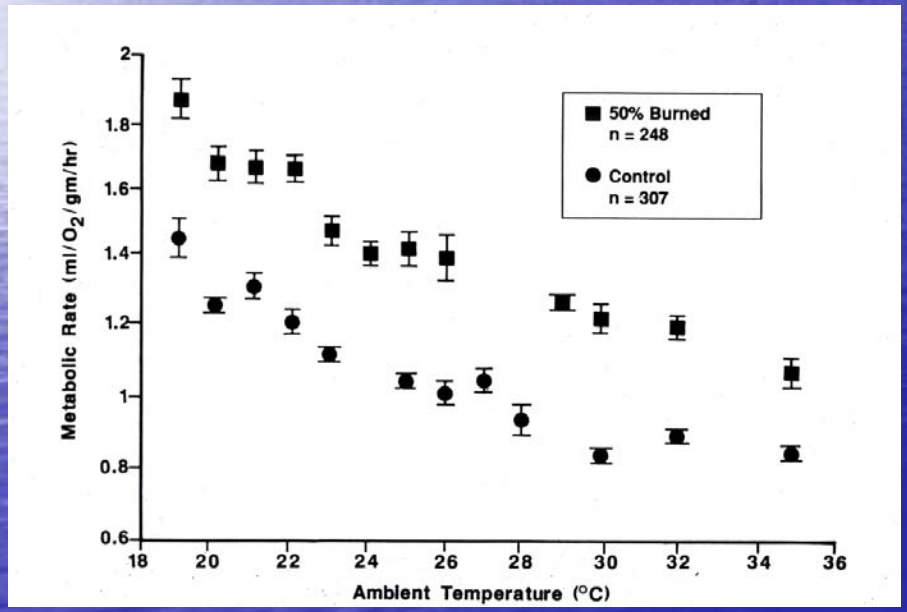
- ABSI correlates better with mortality than APACHE II
- Most nutritional assessment tools are confounded by the inflammatory response in burns Prelack et al. Burns 2007; 33: 13-24.
- The clinical Pulmonary Infection score (CPIS) does not accurately predict the presence of pneumonia in burn patients, due to the systemic inflammation associated with injury Pham et al. J Burn Care Res 2007; 28: 76-9.
- Sepsis definitions should be specific (see next)

Definition of *Sepsis*

- Burn
  - At least 3 of the following:
    - T>38.5 or <36.5°C
    - Progressive tachycardia
    - Progressive tachypnea
    - WBC > 12,000 or <4,000
    - Refractory hypotension
    - Thrombocytopenia
    - Hyperglycemia
    - Enteral Feeding Intolerance
  - *AND*
    - Pathologic tissue source identified

- Modified ACCP/SCCM
  - At least 2 of the following:
    - T>38.5 or <36.5°C
    - HR>20% above NL for age
    - RR>20% above NL for age or $PaCO_2$<32 torr
    - WBC > 12,000 or <4,000
  - *AND*
    - Bacteremia or fungemia
    - Pathologic tissue source identified

Effect of Ambient Temperature on Metabolic Rate



Herndon. Mediators of metabolism. J. Trauma 21:701-705; 1981.

EFFECTS OF BURN INJURY ON IMMUNITY

- Decreased Neutrophils Chemotaxis
- T Cell Numbers Decreased
- Decreased Leukocyte Killing
- B Cell Numbers Normal or Increased
- Immunoglobulin Levels Variable
- Decreased Delayed Hypersensitivity
- Decreased Complement Levels

Burn-Associated Immunosuppression
Associated with

Impairments in microbiocidal activities of:

Natural Killer cells	**Macrophages**
T cells	**Neutrophils**

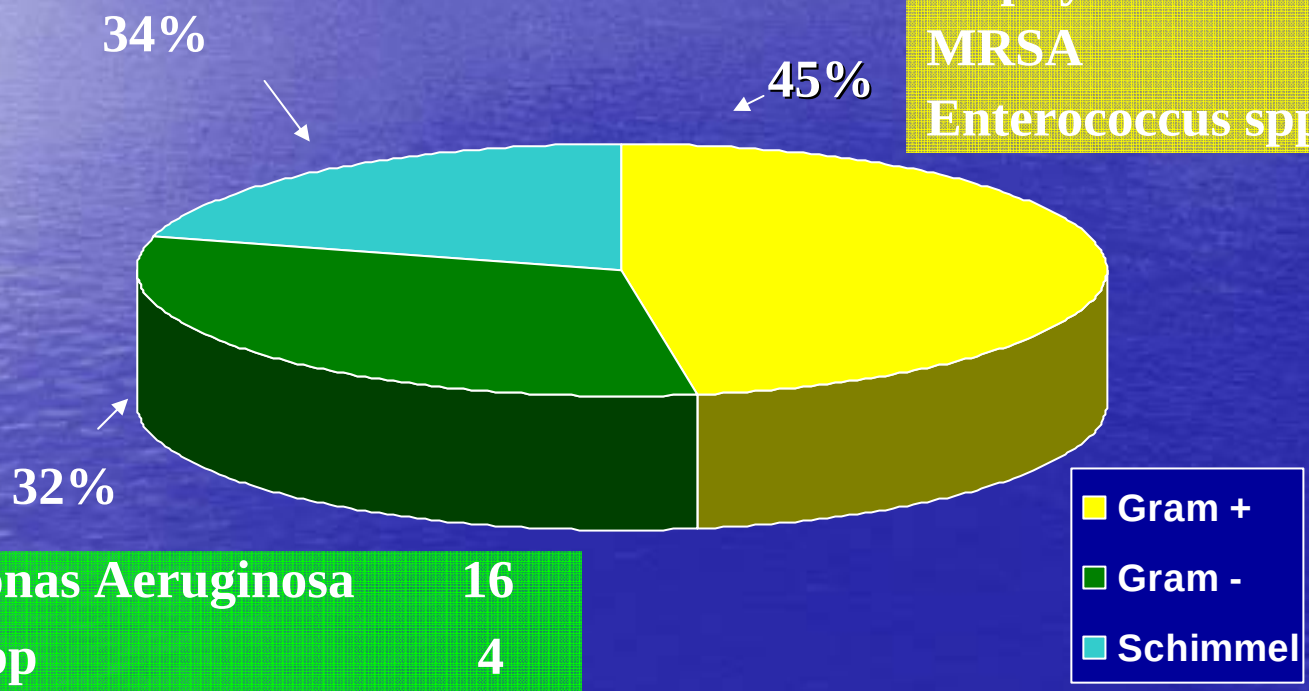
Changes in relative Th1/Th2 cytokine levels

↓ Th1 (IFN-γ, IL-12, IL-15, IL-2)

↑ Th2 (IL-10 and IL-4)

WOUND CULTURES Jan – Mar 01 (N=81)

Staphylococcus aureus	11
Staphylococcus albus	11
MRSA	9
Enterococcus spp	6



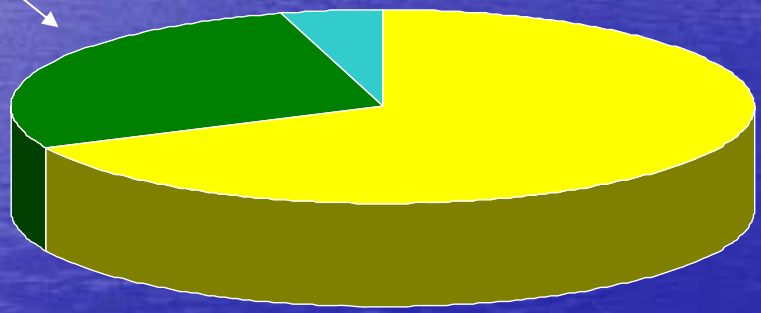
Pseudomonas Aeruginosa	16
Proteus spp	4
Klebsiella spp	3
E. coli	2
Enterobacter spp	1

N = 81

CATHETER CULTURES Jan – Mar 01 (N=22)

Pseudomonas aeruginosa	5
Enterobacter spp	1

27%



68%

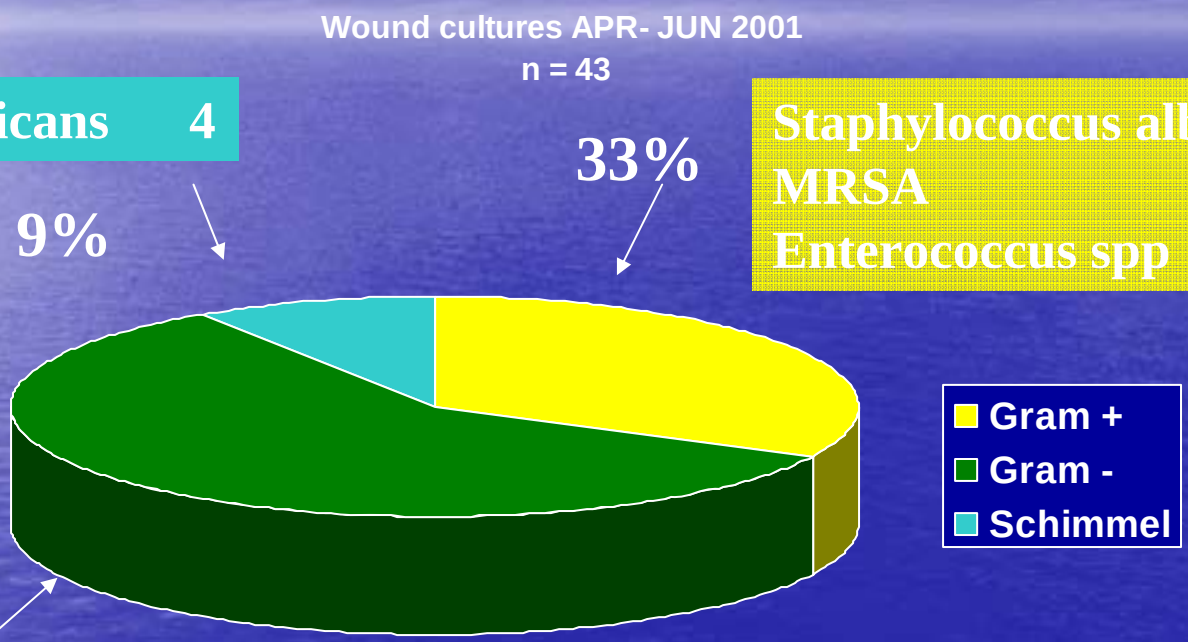
Staphylococcus albus	9
Staphylococcus aureus	3
MRSA	2
Enterococcus spp	1

N = 22

17 venous

5 arterial

WOUND CULTURES Apr– Jun 01 (N=43)

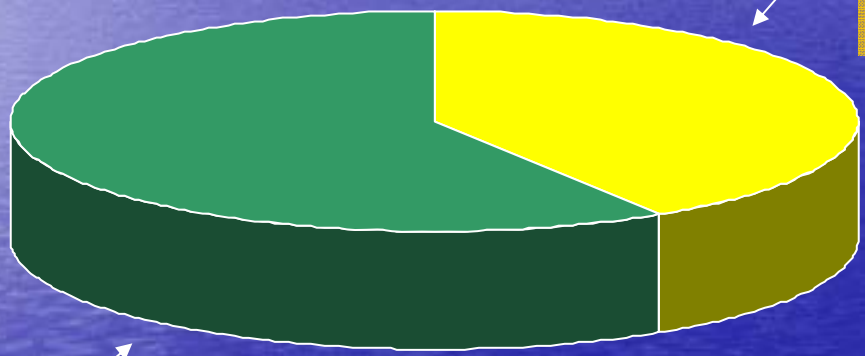


N = 43

CATHETER CULTURES Apr – Jun 01 (N=17)

41%

Staphylococcus albus	5
MRSA	1
Enterococcus spp	1



59%

Pseudomonas aeruginosa	8
Proteus spp	1
E. coli	1

N = 17

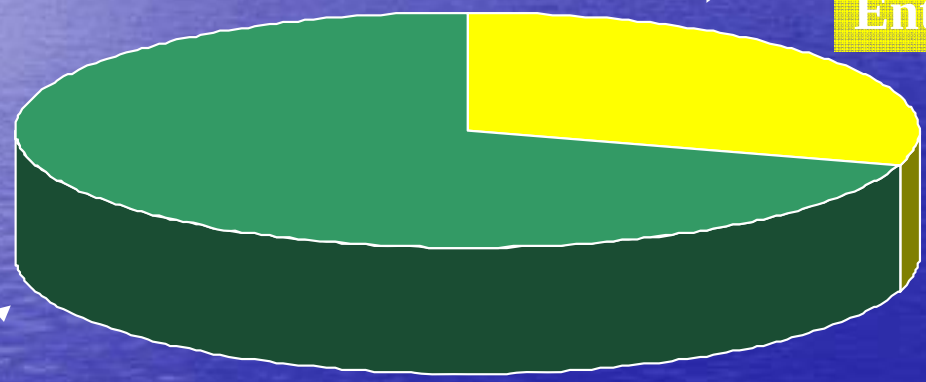
15 venous

2 arterial

WOUND CULTURES Jul - Sep 01 (N=67)

Staphylococcus aureus	4
Staphylococcus albus	7
MRSA	1
Enterococcus spp	8

30 %



70 %

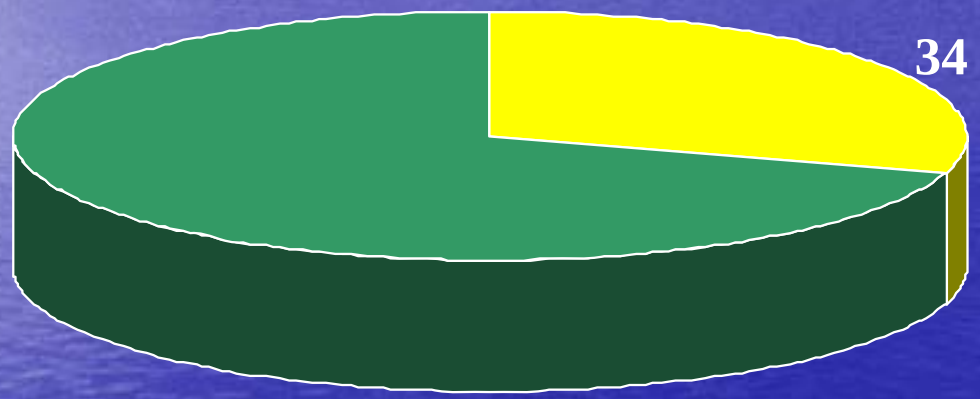
Pseudomonas aeruginosa	20
Proteus spp	8
E. coli	9
Klebsiella spp	5
Enterobacter spp	3
Acinetobacter spp	1

n = 67

CATHETER CULTURES Jul – Sep 01 (N=29)

Staphylococcus aureus	1
Staphylococcus albus	7
Enterococcus spp	2

Candida albicans	1



Pseudomonas aeruginosa	11
Proteus spp	2
Klebsiella spp	2
E. coli	2
Enterobacter spp	1
Acinetobacter spp	1

N = 29

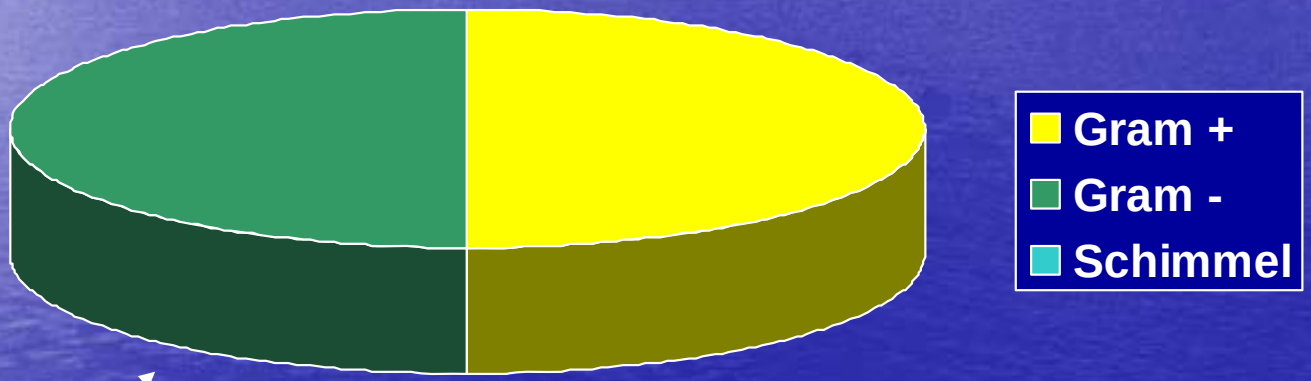
24 venous

5 arterial

WOUND CULTURES Oct - Dec 01 (N=26)

50 %

Staphylococcus aureus	4
Staphylococcus albus	4
Enterococcus spp	5



50 %

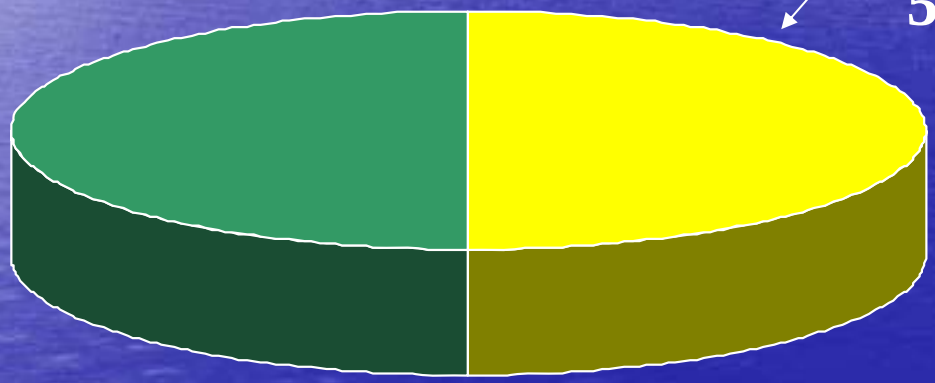
Pseudomonas aeruginosa	6
Proteus spp	2
E. coli	2
Klebsiella spp	1
Enterobacter spp	1
Citrobacter	1

n = 26

CATHETER CULTURES OCT -DEC 01 (N=12)

Staphylococcus aureus	1
Staphylococcus albus	4
Enterococcus spp	2

58 %



42 %

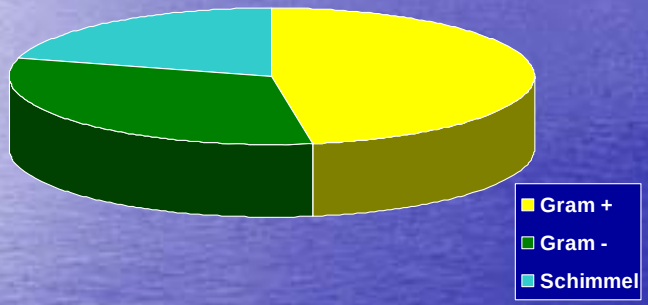
Pseudomonas aeruginosa	4
E. coli	1

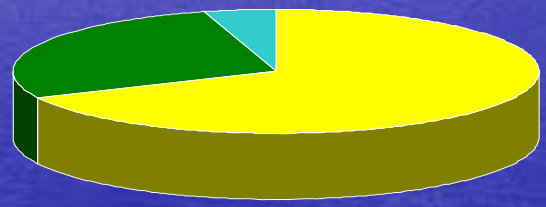
N = 12

11 venous

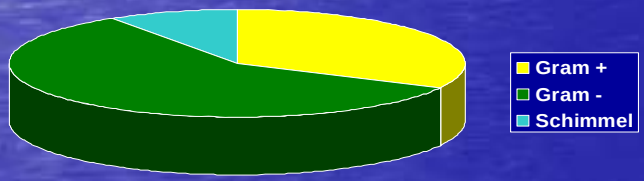
1 arterial

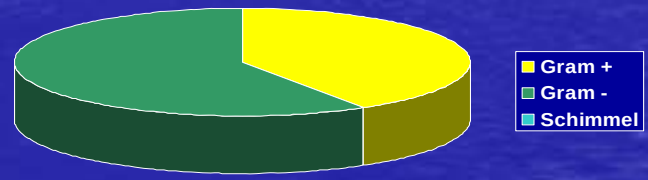
Wound vs Catheter Jan-Jun



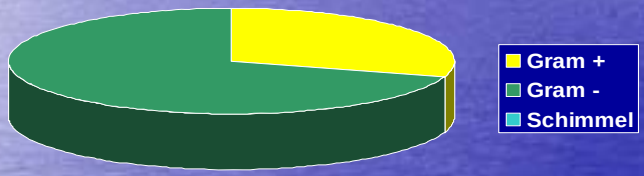


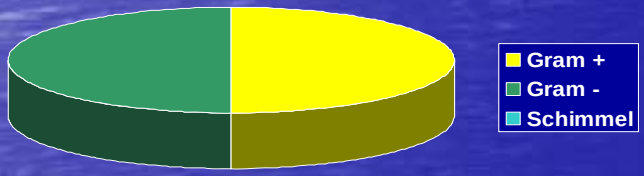
Wound cultures APR- JUN 2001
n = 43

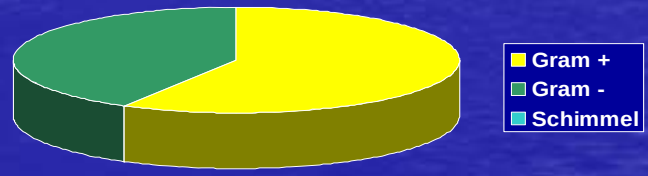




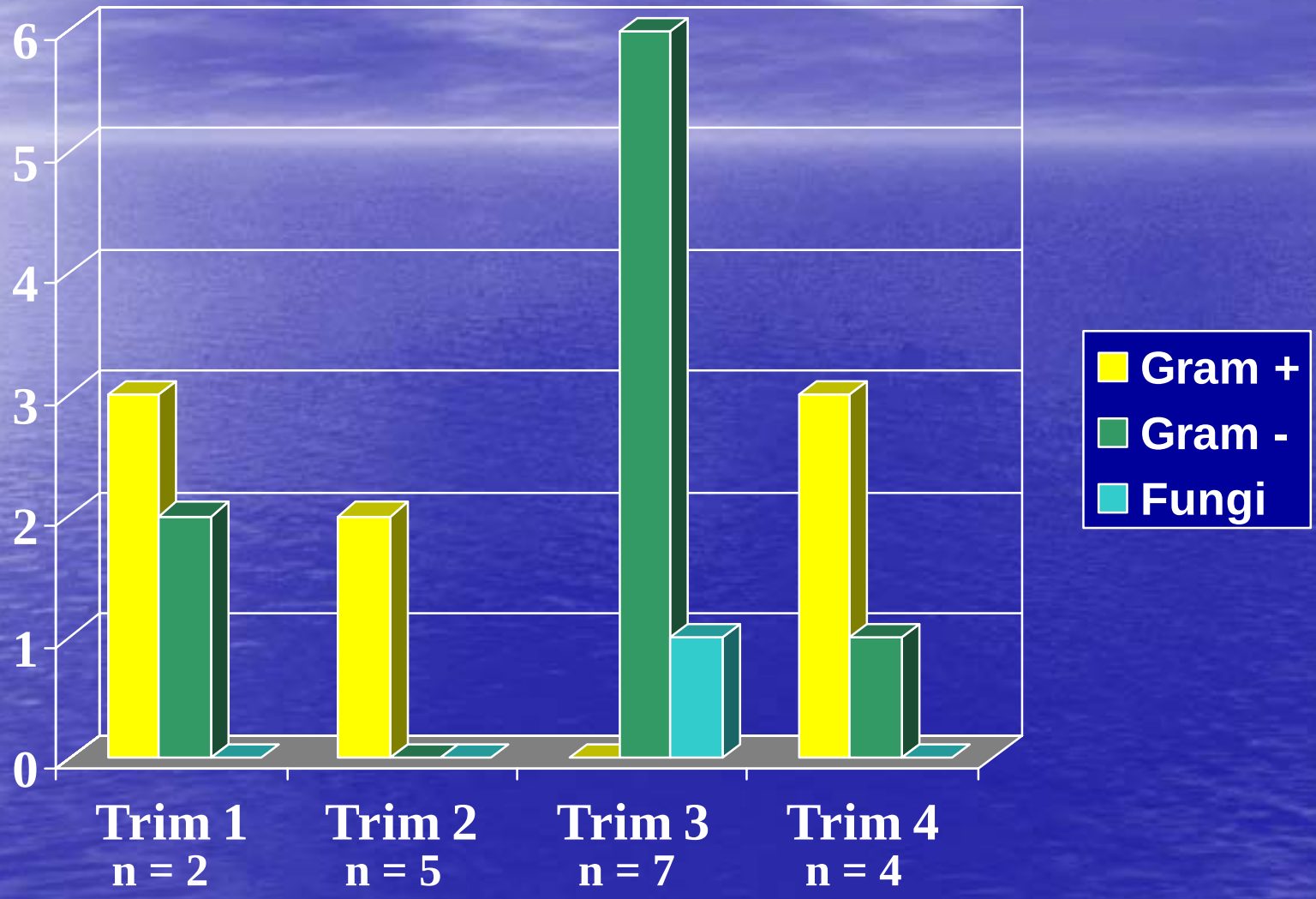
Wound vs Catheter Jul-Dec







HAEMOCULTURES 2001



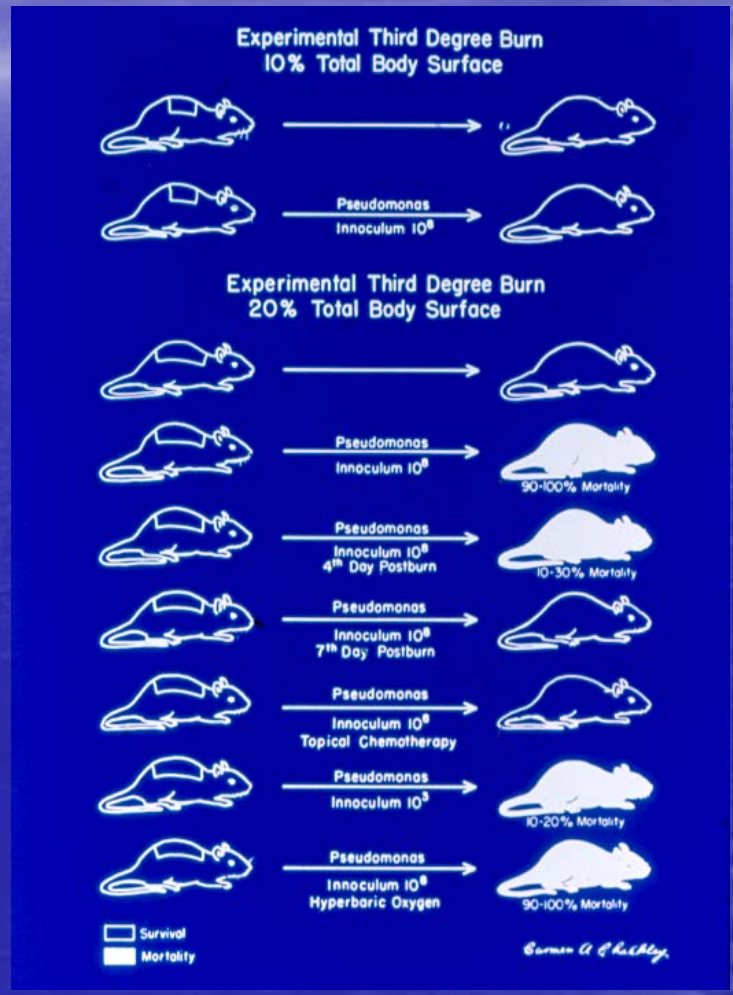
Conclusions

- Skin colonisations correlate with catheters' cultures, both are frequent
- Hemocultures bring few positive results
- The was a shift Gram+/- during the year (was not identical in 2002)
- Conclusions:
  - Aim as 1st priority at reducing the bacterial load on the colonized skin (bath therapy, topical, excision)
  - Treat empirically IV if septic aiming at the germs found in the skin colonization
  - Change catheters if septic and use antimicrobial impregnated catheters

Control of Infection

- Prevention
- Topical Antimicrobials
- Regular cleansing of wounds
- Excision
- Systemic Antimicrobials

Are Topical Antimicrobials Usefull ?



QUANTITATIVE BACTERIOLOGY OF THE BURN WOUND

(AUTOPSY - TOTAL BURN > 50%)

YEAR	NO. CASES	NO. WOUND SAMPLES	BACTERIA PER GRAM TISSUE	
			AVERAGE	RANGE
1963 (NO SULFAMYLON	12	43	6×10^7	10^5-10^9
1964 (SULFAMYLON)	9	38	8.4×10^4	10^2 - 10^5

Invasive Burn Wound Sepsis

Wound Treatment	Incidence as Autopsy Cause of Death
No topical therapy	60%
Topical Therapy	28%
Topical Therapy plus Early Excision	6%

Topical Therapy of the Burn Wound

- Silver Sulfadiazine Cream
- Dressing with Silver Micro-crystals
- Isobetadine (Polyvidon Iod 10%)
- Furacin Solution (Nitrofural 0.2%)
- Colistin Milk (Colistin Sulf 0.5%)

Molecular Epidemiology of *Pseudomonas Aeruginosa* Colonization in the Brussels Burn Unit

Pirnay JP, De Vos D, Cochez C et al. J Clin Microbiol 2003; 41: 1192-1202.

Setting

- ICU: 8 single-bed rooms, MCU: 12 double-bed rooms
- Daily hydrotherapy and Daily application of 1% Silver Sulphadiazine (SSD)
- Surgical excision starting within 1st week after admission
- Sampling: twice a week (ICU), weekly (MCU)
- July 1998 – July 1999: 441 patients (ICU + MCU)
- 5 August 1998: outbreak MDR *Ps. Aeruginosa*
- 1999: epidemic strain disappeared (occupancy rate: 10%)

Outbreak Analysis

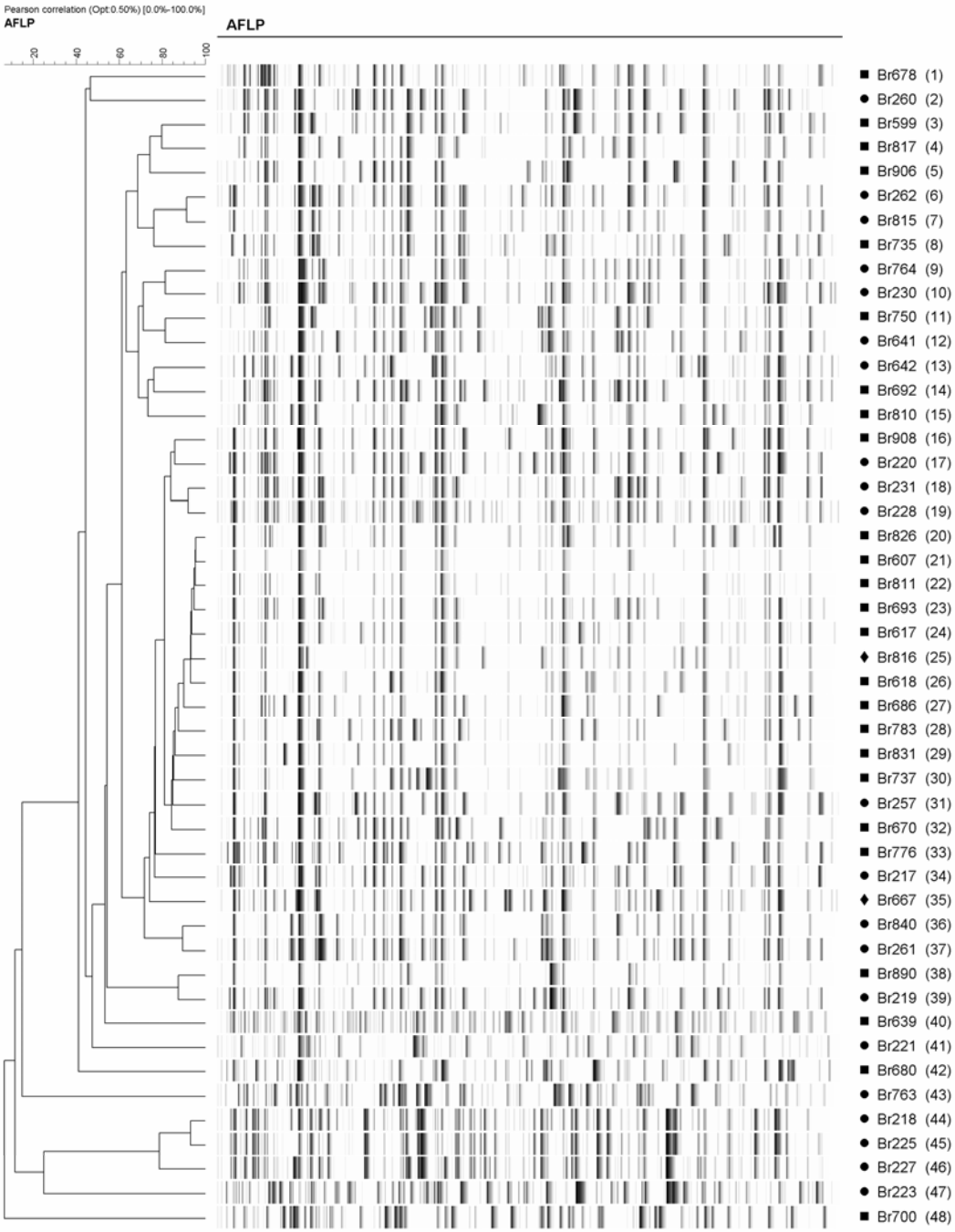
Exogenous source initially suspected

→ Screening of patients

→ Environmental survey

→ Retrospective analysis frozen stock

- **Methods:**
  - Standard microbiology procedures
  - Serotyping and drug susceptibility testing (antibiotics and topical agents)
  - Genotyping: RAPD-PCR and AFLP



366 *Ps. Aeruginosa* isolates (incl. 45 environmental): 48 genotypes

48 AFLP patterns and dendrogram of the *Ps. Aeruginosa* genotypes

DNA genotyping: Results (1)

- 48 different AFLP genotypes - N patient = 70 (100%)
  - 21 exclusively from environment
  - 15 from only one patient
  - 12 from several patients (N = 57), <u>of which 2 in env.</u>

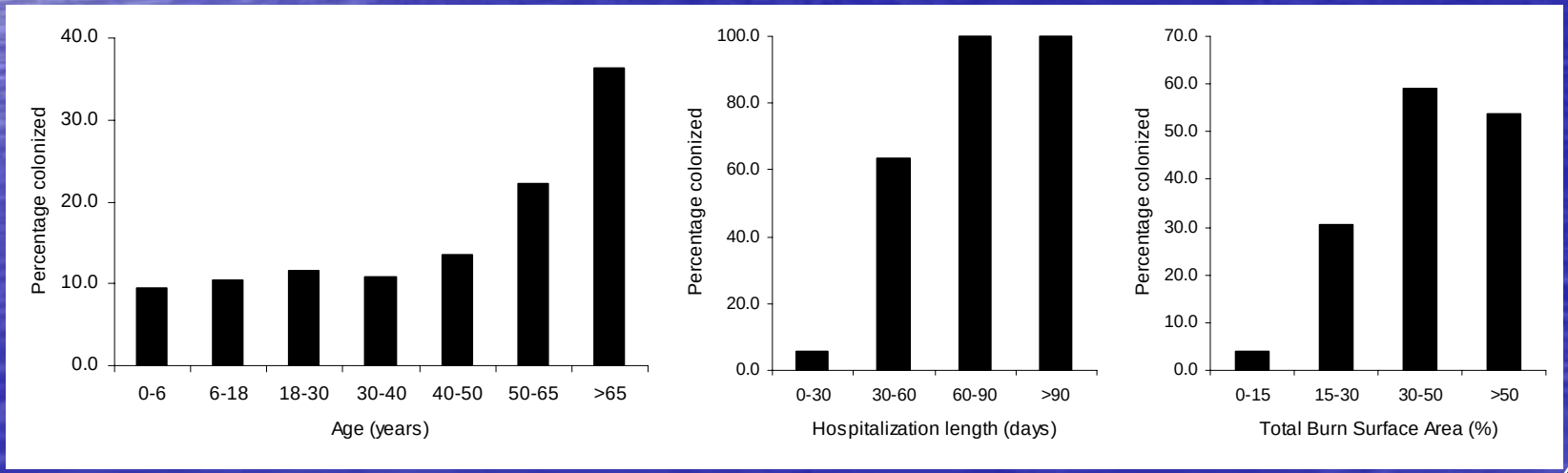
Conclusion:

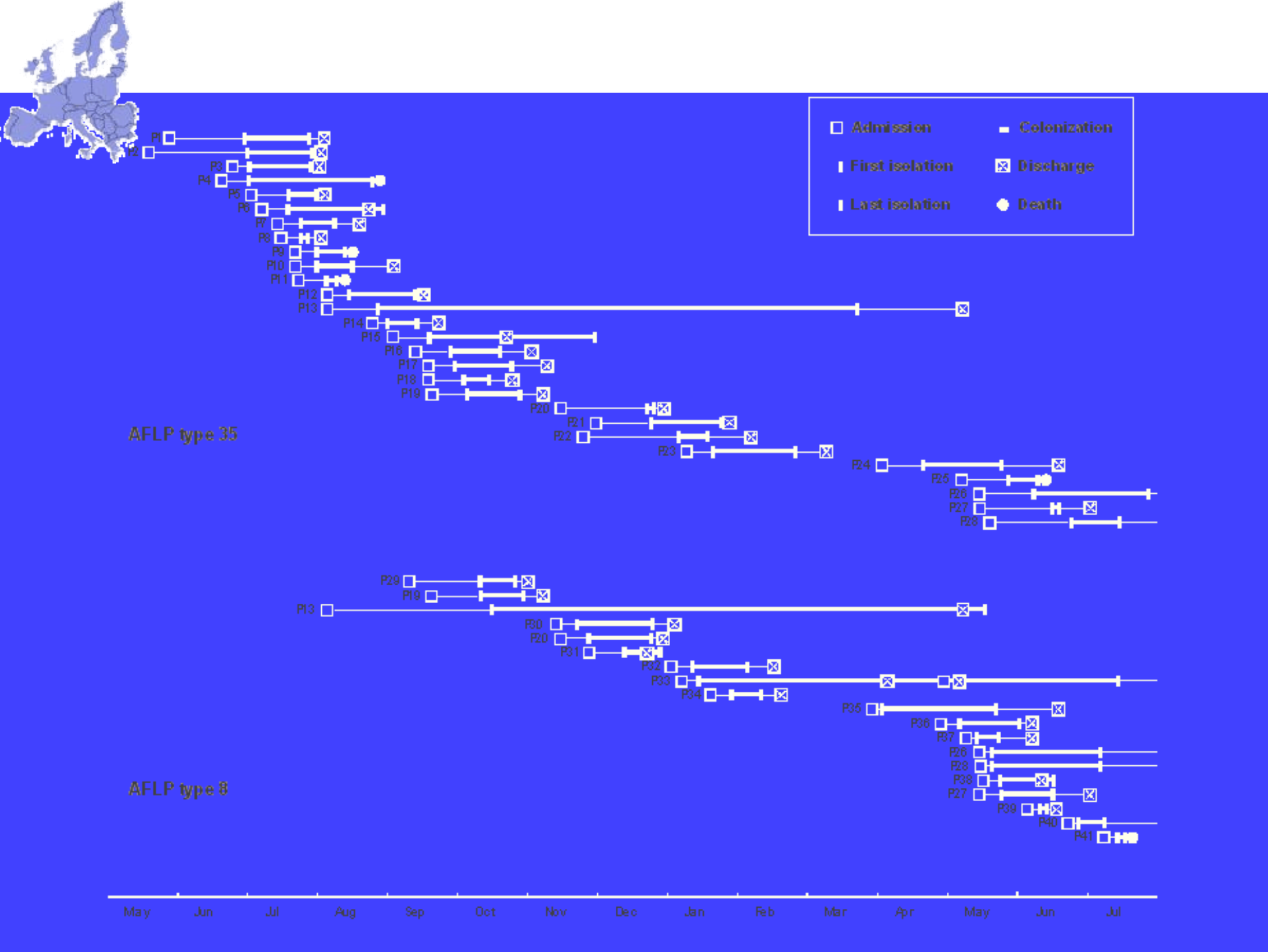
- **No ongoing *Ps. Aeruginosa* reservoir in environment**
- **But, 57 events of cross-acquisition**

- Concentrating on the genotypes found in n patients
  - 27% of the patients colonized by 2 to 4 strains
  - **And, 2 genotypes were found in 60% of the patients**
    - AFLP 35: 131 isolates, 29 patients
    - AFLP 8: 76 isolates, 19 patients

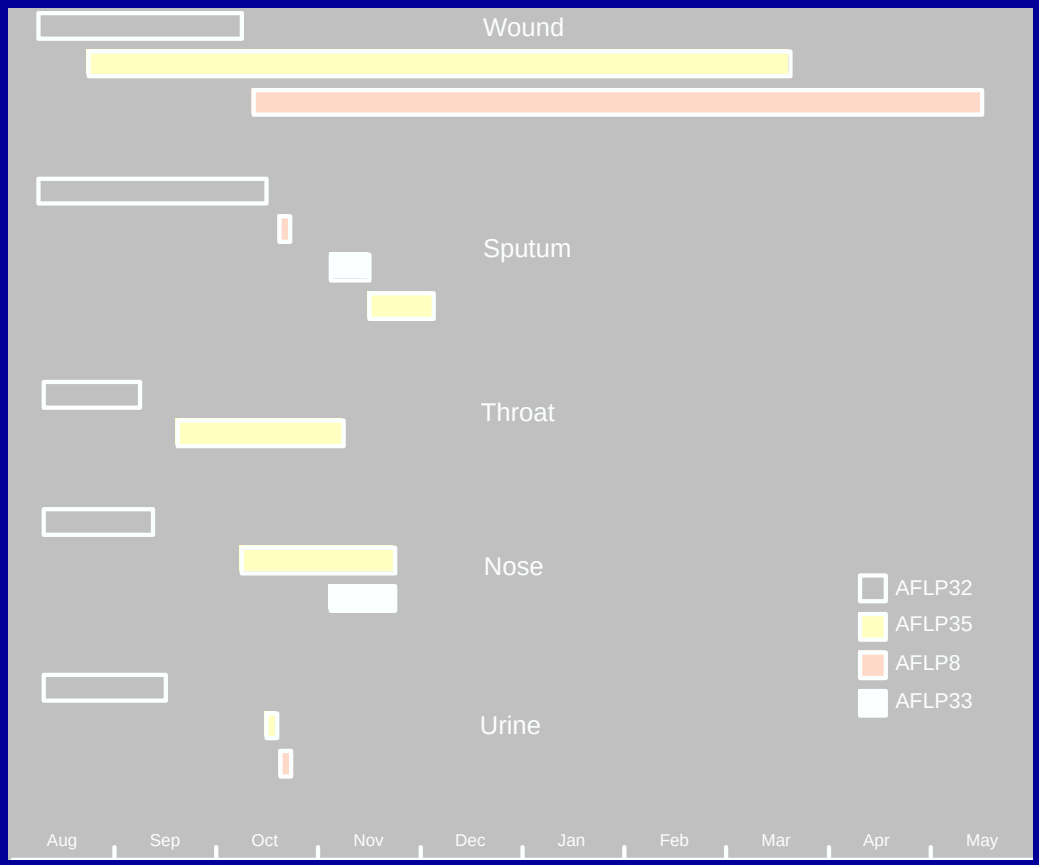
Results (2)

- Characteristics of *P. Aeruginosa* colonized patients
  - **Most of them were colonized in the unit, so the main factor was the length of stay (LOS)**
  - Out of 441 patients, 70 patients (16%) colonized,
  - 12 (17%) at admission, 58 (83%) later (nosocomially)
  - Colonization versus hospitalization length, age and TBSA




Admission
Colonization
First isolation
Discharge
Last isolation
Death
AFLP type 35
AFLP type 8
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Jan
Feb
Mar
Apr
May
Jun
Jul

Patient P13 (age 25, TBSA 75%, 10 month hospitalization)



Simultaneously colonized with 4 genotypes (incl. AFLP 35 and AFLP 8)

Results (3)

- Drug susceptibility testing - AFLP 35 & 8
  - Antibiotics
    - Most strains susceptible to most antibiotics
    - 4 genotypes (incl. AFLP 35) were MDR
  - Topical agents
    - AFLP 8: antibiotic sensitive but SSD^R

Analysis of an Outbreak of *Ps. Aeruginosa*, Conclusions:

- Patient P13: continuous reservoir of AFLP 35 and AFLP 8
- AFLP 35 and AFLP 8 were highly successful (60% of the patients with Ps Ae) due to acquired resistance to antibiotics or topical antimicrobial
- No inanimate reservoir and patients colonized via cross-acquisition

Burn Unit, Brussels

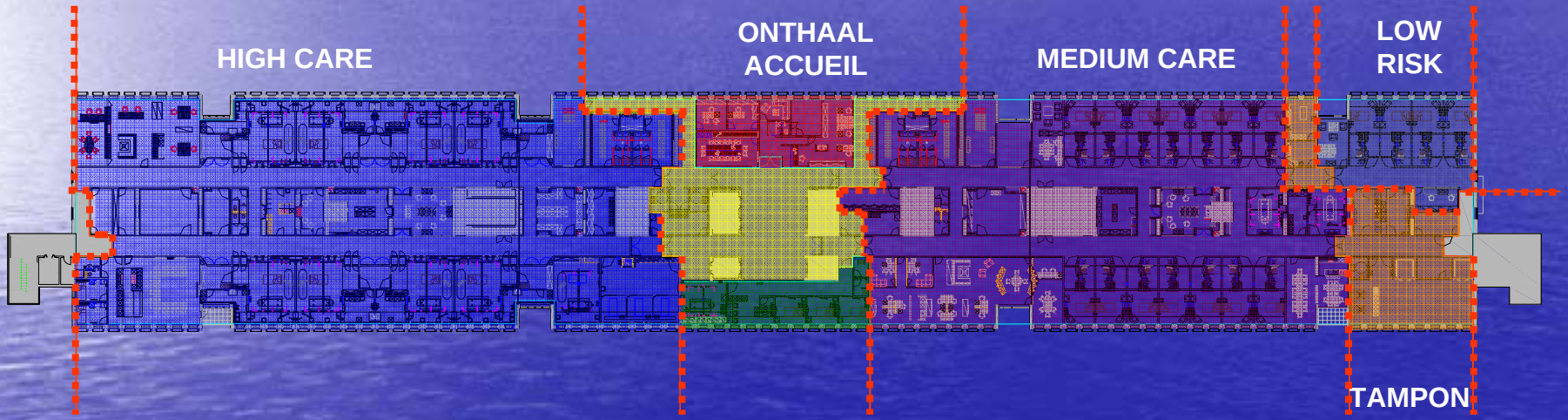
The project for a New Unit:

A burn center must be renovated every 15 years, this means planning and budgeting after ten years…

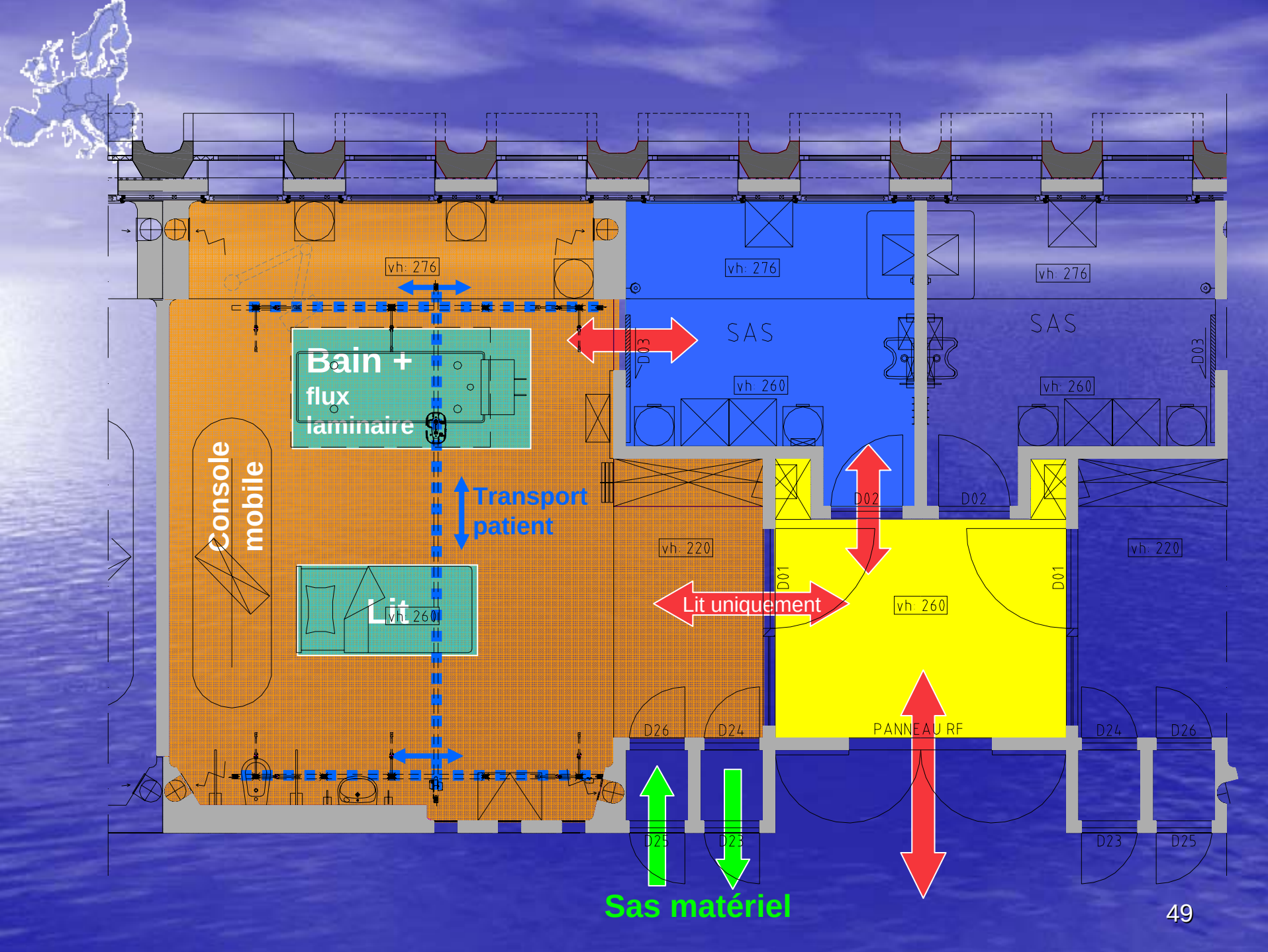
This project was designed to reduce the bacteriological risk.

+5

B4. Medische Organisatie : Algemeen
Organisation Médicale : Généralités



AMBULANTE KLINIEK
–
CLINIQUE PATIENTS AMBULATOIRES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PANNEAU RF
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D25
Sas matériel

Sepsis with MR Ps Aeruginosa

- Colistine IV (Colistineb®) is used (again) since 2006
  - 6-8 Mio./24 Hr in three dosis
  - Toxicity:
    - Follow Renal (RF) function and adjust dosis
    - Toxicity increased by concommittent use of an aminoglycoside
    - In 15% has an impact on RF (reversibility)
    - In 4-6% is neurotoxic (reversibility and not dosis related)
  - From in vitro studies: the parenteral form and long dosage intervals may be problematic for treatment of infections by colistin resistant A. baumanii

    Owen et al. J Antimicrob Chemother. 2007 Feb 8.

Centre des grands brûlés

Acknowledgements

- Slides 3-14, 16-20 : D HERNDON, MD
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- Slides 39-47: JP PIRNAY, PhD
- Slides 49-50 : S WEYGERS