Prevention of Infectious Diseases in the Immunocompromised Host

Anne Friedland, MD

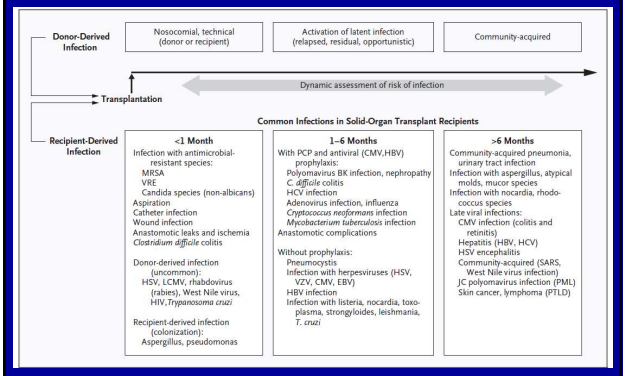
1

Overview

- Solid organ transplantation
- Stem cell transplantation
- Neutropenia
- Burns

2

Timeline of Infectious Risk



Fishman. NEJM 2007;357:2601

3

Viral Infections post Transplant

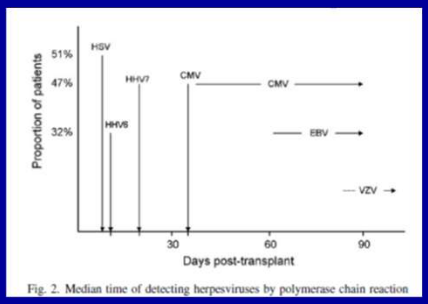
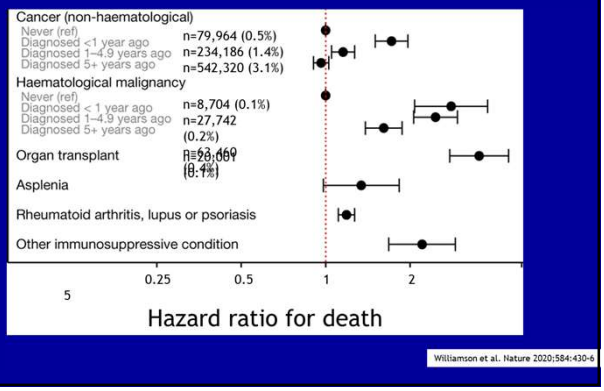


Fig. 2. Median time of detecting herpesviruses by polymerase chain reaction

Griffiths. Antiviral Res 2006;2-3:192

4

Outcomes after COVID-19



Williamson et al. Nature 2020;584:430-6

5

Risk for infection after SOT

- Exposures
  - Donor-derived
  - Recipient-derived
  - Nosocomial
  - Community
- "net state of immunosuppression"

Fishman. NEJM 2007;357:2601

6

Donor-derived infections

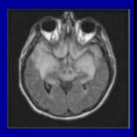
Table 1
Potential donor-derived infectious diseases transmissions reported to the OPTN, 2005–2009

Disease	Number of Donor Reports	Number of Recipients with Confirmed Transmission	Number of DDD-Attributable Recipient Deaths
Virus	86	31	8
Bacteria	38	26	7
Fungus	30	26	8
Mycobacteria	26	10	2
Parasite	21	13	4
Total infections	201	106	29

Chong et al. Inf Dis Clin N Am 2013;27:253

7

Unusual donor-derived infections



- Rabies
  - 1 donor, 4 recipients: 100% mortality
- West Nile Virus
  - 2 donors, 8 recipients: 1 death, 2 coma
- Lymphocytic choriomeningitis virus
  - 2 donors, 8 recipients: 88% mortality
  - LCMV could not be detected in either donor
  - 1 donor had pet hamster with LCMV
- Balamuthia mandrillaris
  - 2 donors, 8 recipients: 2 deaths, 1 neuro sequalae

Srinivasan et al. NEJM 2005;352:1103
Chong et al. Inf Dis Clin N Am 2013;27:253

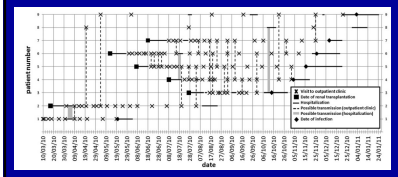
8

Nosocomial infections

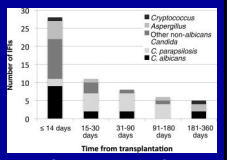
- Device-related
  - Line-associated blood stream infection
  - Catheter or stent associated UTI
  - Ventilator associated pneumonia
- Surgery-related
  - Wound infection
  - Intra-abdominal abscess
- Outbreaks
- Multi-drug resistant organisms

9

Outbreaks



Pneumocystis in pediatric renal transplant recipients

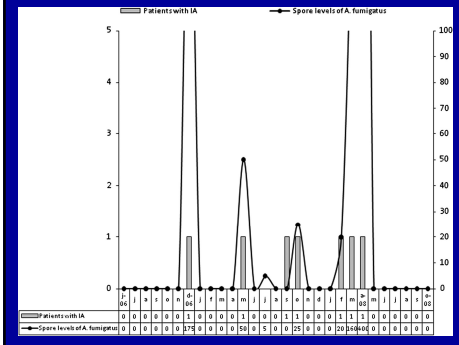


C. parapsilosis after liver transplantation

Raghuram et al. Liver Transplant 2012;18:1100
Brunot et al. Transplant Proc 2012;44:2818

10

Aspergillus in heart surgery ICU



3 heart transplant recipients developed invasive aspergillosis

2/3 died

Poláez T et al. Clin Infect Dis. 2012;54:e24-e31

11

Mold in the walls….

12

Community acquired infections

- Immunosuppression does not prevent common infections…
- Manifestations may be different
- Common pathogens include:
  - Respiratory viruses
  - Skin flora (*S. aureus*, streptococci)
  - Enteric flora (GNR, enterococci)

13

S. aureus bacteremia post-SOT

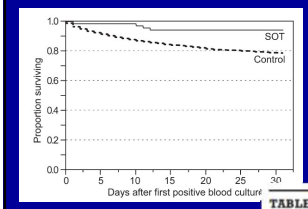


TABLE 3. Cox proportional hazards analysis 30-day mortality in entire SAB cohort (n = 2959)

Variable	RR (95% CI)	P
Age	1.03 (1.02–1.03)	<0.001
Methicillin resistance	1.21 (1.03–1.41)	0.02
SOT recipient	0.37 (0.11–0.88)	0.02

SAB: S. aureus bacteremia. SOT: solid organ transplant recipient.

Malinis et al. Transplantation 2012;93:1045

14

Net State of Immuno-suppression

- Type, dose, and timing of immunosuppressive agents administered
- Nutritional, metabolic factors; renal dysfunction; age; comorbidities
- Breach of mucosal barriers (skin, gut); foreign bodies
- Hypogammaglobulinemia
- Neutropenia

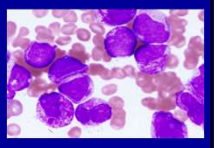
15

Overview

- Solid organ transplantation
- Stem cell transplantation
- Neutropenia
- Burns

16

Indications: malignancy



- Hematologic malignancies
  - Leukemias
  - Lymphoma
  - Multiple myeloma
  - Myelodysplastic/myeloproliferative syndromes
- Selected solid malignancies
  - Renal cell carcinoma
  - Ewing sarcoma
  - neuroblastoma

Tallman et al. Blood 2009;114:5126

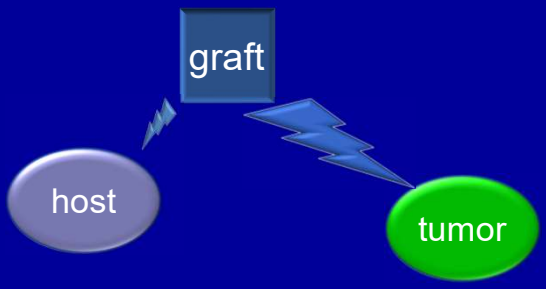
17

HSCT: other indications

- Acquired
  - Aplastic anemia
  - Paroxysmal nocturnal hemoglobinuria
  - Auto-immune disorders
- Congenital
  - Immunodeficiency syndromes (e.g. SCID)
  - Hemoglobinopathies
  - Congenital anemias
  - Storage diseases
  - Bone marrow failure syndromes
  - osteoporosis
- HIV

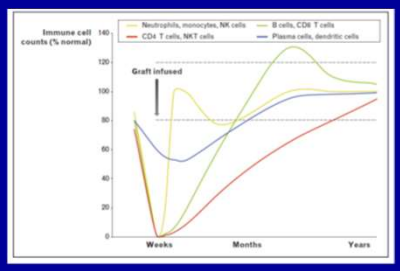
18

HSCT principles: maximizing graft vs tumor while minimizing graft vs host effects



19

Immune reconstitution after HSCT

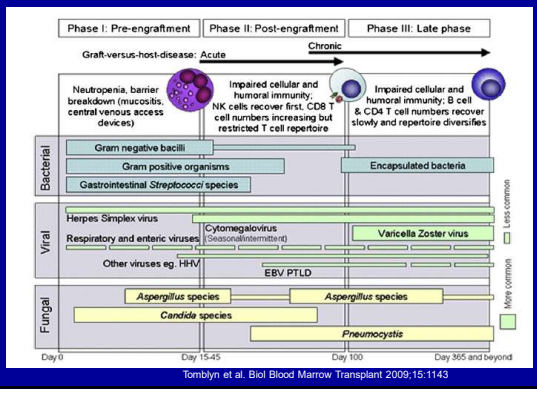


--B cells, CD8 T cells
--Neutrophils, monocytes, NK cells
--plasma cells, dendritic cells
--CD4 T cells, NKT cells

Bosch et al. Curr Opin Hematol 2012;19:324

20

Timeline of infections



Tomblyn et al. Biol Blood Marrow Transplant 2009;15:1143

21

Infectious risk

	Higher risk	Lower risk
Transplant	allogeneic	autologous
Type of donor	Unrelated	related
HLA matching	HLA mismatch	HLA match
Stem cell source	Cord blood	Peripheral blood
Graft manipulation	T cell depletion	No manipulation
Conditioning regimen	Full intensity	Reduced intensity
immunosuppression	T cell depleting agents	Minimal IS
GVHD	Moderate-severe	None or mild

Wingard et al. Inf Dis Clin N Am 2010;24:257

22

Graft vs Host Disease

- GVHD requiring treatment seen in 40% of HLA-matched allo-HSCT recipients
- Acute GVHD
  - Skin: pruritic maculopapular rash
  - GI tract: nausea, abd pain, diarrhea
  - Liver: cholestasis
- Graded based on extent of end-organ ir
  - I mild
  - II moderate
  - III severe (~25% 5-year survival)
  - IV very severe (~5% 5 year survival)

Ferrara et al. Lancet 2009;273:1550

23

Treatment of GVHD

- Steroids remain first line
  - Topical for skin and lung (inhaled)
  - Systemic for more severe disease and other target organs
- Calcineurin inhibitors may be added
- Steroid-refractory GVHD important concern
  - Alternative approaches under investigation
    - Imatinib (platelet-derived growth factor signaling inhibition)
    - Sirolimus (mTOR inhibition)
    - Ex vivo cellular manipulation (e.g. tolerogenic DC induction)
    - Bortezomib (proteasome inhibition)

24

Bacterial infections after HSCT

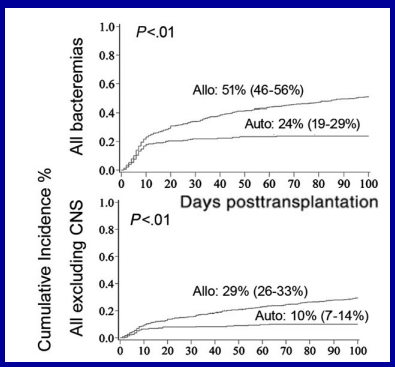
Table 2
Types of infections encountered at various times after HSCT

Type of Infectious Pathogen	Early Preengraftment (First 2–4 wk)	Early Postengraftment (Second and Third Month)	Late Postengraftment (After Second or Third Month)
Bacteria	Gram-negative bacteria (related to mucosal injury and neutropenia) Gram-positive bacteria (related to venous catheters) *Clostridium difficile* (related to neutropenia, antibiotics, antiacid medications)	Gram-positive bacteria (related to venous catheters) Gram-negative bacteria (related to enteric involvement of GVHD, venous catheters)	Encapsulated bacteria (related to poor opsonization with chronic GVHD) *Nocardia* (related to chronic GVHD)

Wingard et al. Inf Dis Clin N Am 2010;24:257

25

Bacteremia



Bock et al. Biol Blood Marrow Transplant 2013;19:102

26

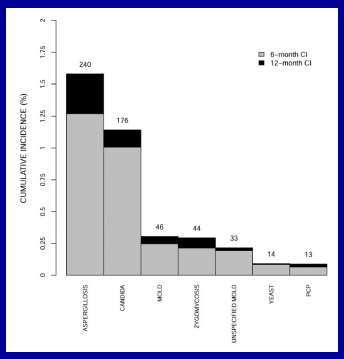
Table 2
Types of infections encountered at various times after HSCT

Type of Infectious Pathogen	Early Preengraftment (First 2–4 wk)	Early Postengraftment (Second and Third Month)	Late Postengraftment (After Second or Third Month)	Time Independent
Fungi	*Candida* (related to mucosal injury and neutropenia)	*Aspergillus*, other molds and *Pneumocystis jirovecii* (related to GVHD)	*Aspergillus*, other molds and *P jirovecii* (related to GVHD)	
Herpesviruses	HSV	CMV (related to GVHD and impaired cellular immunity) EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)	CMV and VZV (related to GVHD and impaired cellular immunity and viral latency before transplant) EBV (in patients who have T-cell depleted grafts, receive ATG, or whose donor is mismatched)	
Other viruses		BK virus (related to GVHD and cyclophosphamide in conditioning regimen)		Respiratory viruses (temporally tracks with community outbreaks) Adenoviruses

Wingard et al. Inf Dis Clin N Am 2010;24:257

27

Incidence of fungal infections



Kontoyiannis et al. CID 2010;50:1091

28

Aspergillus outbreak in HSCT

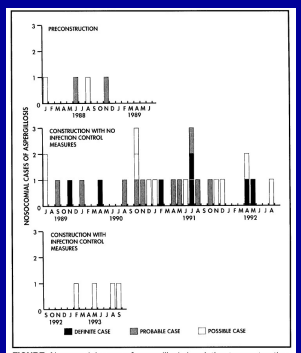


FIGURE. Nosocomial cases of aspergillosis in relation to construction.

Loo et al. ICHE 1996:360-36

29

Overview

- Solid organ transplantation
- Stem cell transplantation
- Neutropenia
- Burns

30

Febrile Neutropenia

Multinational Association for Supportive Care in Cancer study

- Prospective observational study
- N=1,139
- Bacteremia documented in 26%
- Outcomes:
  - Resolution: 84%
  - Alive with at least one serious complication: 11%
  - Death: 5%

Klastersky et al. J Clin Oncol 2000;18:3038

31

IDSA GUIDELINES

Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer: 2010 Update by the Infectious Diseases Society of America

Alison G. Freifeld,[1] Eric J. Bow,[2] Kent A. Sepkowitz,[3] Michael J. Boeckh,[4] James I. Ito,[5] Craig A. Mullen,[3] Issam I. Raad,[6] Kenneth V. Rolston,[6] Jo-Anne H. Young,[7] and John R. Wingard[8]

Table 2. Strength of Recommendation and Quality of Evidence

Category/Grade	Definition
Strength of Recommendation	
A	Good evidence to support a recommendation for *or against* use.
B	Moderate evidence to support a recommendation for *or against* use.
C	Poor evidence to support a recommendation.
Quality of Evidence	
I	Evidence from >1 properly randomized, controlled trial.
II	Evidence from >1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Freifeld et al. CID 2011;52:e5

32

Guideline recommendations

- High risk
  - Prolonged (anticipated >7 days) and profound neutropenia (≤100 cells/mm^3)
  - "comorbid medical problems"
    - Hypotension
    - Pneumonia
    - New abdominal pain or new GI symptoms
    - Neurologic changes
    - Line infection
    - Severe mucositis
  - Hepatic or renal insufficiency

Freifeld et al. CID 2011;52:e56

33

MASCC score: less is worse

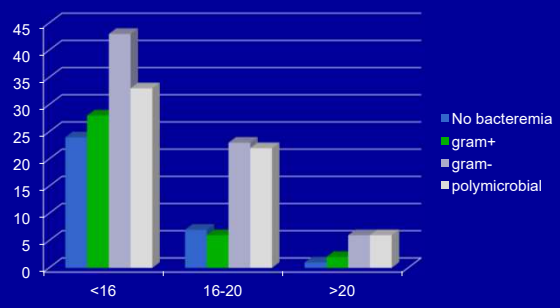
Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms[a]	5
No hypotension (systolic blood pressure >90 mmHg)	5
No chronic obstructive pulmonary disease[b]	4
Solid tumor or hematologic malignancy with no previous fungal infection[c]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[a]	3
Outpatient status	3
Age <60 years	2

- 26 maximum score -> lowest risk
- <21 considered high risk

Freifeld et al. CID 2011;52:e56

34

Mortality risk by MASCC score



Paesmans et al. Support Care Cancer 2011;19:1001

35

Risk determines initial treatment

High risk patients…

- Require hospitalization
- Require initial IV antibiotics
- Most commonly HSCT preparation or acute leukemia induction chemotherapy

Low risk patients…

- May be treated as outpatients
- May be considered for oral antibiotics
- Most commonly solid tumors

Freifeld et al. CID 2011;52:e56

36

ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS , IDSA 2011

- General
  - **Hand hygiene**
  - **Standard barrier precautions and infection specific precautions**
  - **HSCT recipients should be housed in private rooms. Allogeneic HSCT recipients should be housed in rooms with >12 air exchanges/h and HEPA filtration**
  - **Plants and dried or fresh flowers should be prohibited**
  - **Hospital work exclusion policies should be designed to encourage HCP to report their illnesses or exposures**

37

ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS , IDSA 2011

- Neutropenic diet
  - **Consists of well cooked foods**
  - **Prepared luncheon meats should be avoided**
  - **Well cleaned, uncooked raw fruits and vegetables are acceptable, as are cooked foods brought from home or restaurants, provided that the freshness of ingredients and means of preparation can be confirmed**

38

ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS , IDSA 2011

- Patient skin and oral care
  - **Patients should take daily showers or baths**
  - **Skin should be inspected daily**
  - **Gentle but thorough perineal care after bowel movement**
  - **Avoid rectal thermometers, enemas, suppositories, and rectal exams**
  - **Menstruating females should avoid tampons**
  - **Patients with ongoing mucositis should perform oral rinses 4-6 times per day with sterile water, normal saline, or sodium bicarbonate**
  - **Patients with brush their teeth ≥2 times/day with a soft regular toothbrush**
  - **Avoid fixed orthodontic appliances and space maintainers**

39

ENVIRONMENTAL PRECAUTIONS IN MANAGING FEBRILE NEUTROPENIC PATIENTS, IDSA 2011

- Plants and animals
  - **Avoid plants and dried or fresh flowers**
  - **Do not allow visitation by pets (including pet therapy)**
- HCP personnel and visitors
  - **Vaccination of HCP or visitors who are symptomatic with infections transmitted by air, droplet, and direct contact (e.g., VZV, infectious gastroenteritis, HSV lip lesions, URI) should not engage in patient care or visit patients unless appropriate barrier (e.g., mask and glove) protection is established**
- Infection control surveillance
  - **Do not routinely perform bacterial surveillance cultures of the environment, equipment, or devices**

40

ENGINEERING CONTROLS

- *Aspergillus* prevention
  - Filtered hospital air
  - Barrier protection during renovation or construction
  - Protective isolation (HEPA filtered) for hematopoietic stem cell transplants
  - Provide respiratory protection when patients must leave PE
- *Legionella* prevention
  - Prohibit showers (use sponge baths)
  - Implement surveillance for *Legionella* cases
  - Monitor water supply: if *Legionella* present initiate decontamination (controversial)

41

PROCEDURES DURING CONSTRUCTION & RENOVATION

- Seal hospital construction areas behind impervious barriers
- Clean construction area daily (i.e., remove dust with HEPA vacuum)
- Assure that ventilation system does not transport dust from inside construction area to other locations
- Move immunocompromised patients from adjacent areas
- Thoroughly clean construction area prior to patient use
- Conduct surveillance for airborne fungal infections
- Assess airborne fungal levels adjacent to construction
- Avoid transporting construction material through patient areas
- Assess compliance with infection control guidelines

42

Overview

- Solid organ transplantation
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43

Prevention of Infection in Burns

- Topical agents
- Systemic antimicrobial prophylaxis
- Wound care
- Universal isolation precautions
- Frequency of line changes

44

Nosocomial infection in burns

Table 3. Risk factors for development of NI

	Univariate Analysis			Multiple Analysis Model		
	Odds Ratio	95% CI	*P*	Odds Ratio	95% CI	*P*
Sex						
Male	1					
Female	1.02	0.69–1.49	.94			
Age	1.01	0.99–1.01	.163			
Underlying disease						
No	1					
Yes	1.61	0.96–2.69	.07			
Injury						
Scald	1					
Flame	3.48	2.32–5.22	<.001			
Electrical	1.58	0.87–2.87	.14			
Contact	1.38	0.57–3.37	.48			
%TBSA	1.05	1.04–1.06	<.001	1.05	1.04–1.06	<.001
ABSI*	1.44	1.33–1.56	<.001			
Admission day						
≤24 hr	1					
>24 hr	0.11	0.04–0.30	<.001			
Trauma						
No	1					
Yes	0.99	0.29–3.32	.98			
First excision day	1.14	1.10–1.18	<.001	1.13	1.09–1.17	<.001
Transfusion						
No	1					
Yes	5.01	3.29–7.63	<.001			

Alp et al. Burn Care Res 2012;379

45

Combat Burn Guidelines 2011

TABLE 2. Management of Burn Wounds Based on Depth[16,17,20,52–55,58,59]

Wound	Interventions
First degree	Symptomatic care
Superficial partial thickness	Topical antibiotics with twice-daily dressing change, silver-impregnated dressing changed every 3–5 d, or Biobrane*
Deep partial thickness	Topical antibiotics with twice-daily dressing change, or silver-impregnated dressing changed every 3–5 d and excision and grafting
Full thickness	Topical antibiotics with twice-daily dressing change and excision and grafting

* Recommend restriction to individuals experienced with its use.

TABLE 3. Topical Antimicrobial Agents[43,58–63,65–67,71–73]

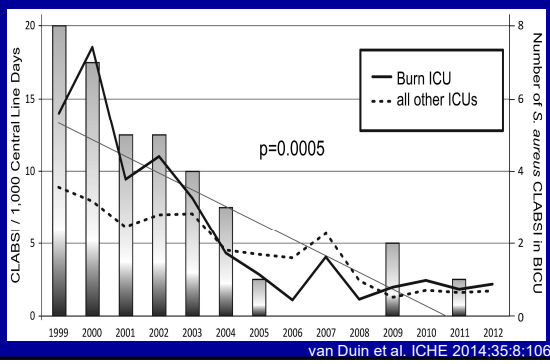
Agent	Application	Penetration	Side Effects
Mafenide acetate cream	Apply 1/16 inch layer twice daily*	Penetrates eschar	Painful on application, metabolic acidosis
Silver sulfadiazine cream	Apply 1/16 inch layer twice daily*	Poor eschar penetration	Transient leucopenia
Silver nitrate solution	Dress wounds with multiple layers of coarse gauze and apply solution to keep gauze continually moist	Poor eschar penetration	Electrolyte disorders
Acticoat, Silverlon, or Silversel†	Moisten dressing with sterile water, cut to size, secure to wound with secondary dressing, change in 3–5 d	Poor eschar penetration	

* Consider alternating mafenide in the morning with silver sulfadiazine in the evening.
† Application information obtained from package insert.

D'avignon et al. J Trauma 2011;S282

46

Decline in the Rate of Bloodstream Infections



van Duin et al. ICHE 2014:35:8:1066-68

47

Interventions to Decrease CLABSI Rate at UNC

TABLE 1. Interventions to Reduce Central Line–Associated Bloodstream Infections (CLABSIs) at University of North Carolina Hospitals, 2000–2009

Year(s)	Intervention(s)
2000	Enhanced education of medical staff regarding central lines; addition of 2% chlorhexidine plus 70% isopropyl alcohol for skin preparation to central line kits
2001	Mandatory training for nurses on IV line site care and maintenance
2003	Central line changes over a guidewire every 3 days with use of a new site every 6 days becomes standard practice; use of full body drape for line insertion and changes
2003–2005	Introduction of antibiotic-impregnated central venous catheters for all patients
2004	Enhanced nursing education on central line insertion and maintenance
2005	Customized catheter-insertion kits
2006	Universal glove and gown use for all patient encounters
2007	Implementation of the Institute for Healthcare Improvement bundle to prevent CLABSI
2009	Use of chlorhexidine patch at insertion site

★ Specific to burn ICU

van Duin et al. ICHE 2014:35:8:1066-68

48

Questions?

49