DEVELOPMENT TOWARDS A PRELIMINARY 'RISK PREDICTION HAZARD MODEL' FOR NOSOCOMIAL INFECTION IN ADULT INTENSIVE CARE UNITS IN MALAYSIA

SUPALETCHIMI GOPAL KATHERASON

UNIVERSITI SAINS MALAYSIA

2010

DEVELOPMENT TOWARDS A PRELIMINARY 'RISK PREDICTION HAZARD MODEL' FOR NOSOCOMIAL INFECTION IN ADULT INTENSIVE CARE UNITS IN MALAYSIA

By

SUPALETCHIMI GOPAL KATHERASON

Thesis submitted in fulfillment of the requirements

for degree of

Doctor of Philosophy

August 2010

DEDICATIONS

The needs of patients in ICU with nosocomial infection including my late father, for quality preventive care have been a great source of inspiration and motivation for me to undertake this study.

This thesis is also dedicated to all healthcare workers in Malaysia who believe in the richness of learning and acquisition of new knowledge put into good clinical practice.

ACKNOWLEDGEMENT

I would like to thank my chief supervisor, Professor Asma Ismail, for her continuous valuable guidance, insightful suggestions, and constant support as well as for her motivation, belief and trust in me to complete this study successfully.

I would also like to show my appreciation to all my co-supervisors for their assistance throughout my study period, especially to Associate Professor Kamarudin Jaalam who continuously gave me emotional support and encouraged me throughout the course of this study. He played a major role in the clinical area in verifying the diagnosis of NI and teaching me the skills in diagnosis especially reading chest X-rays for VAP. He took the time to proof read and edit my thesis from the first draft copy till the final thesis. He also guided me in my write up of manuscripts for publication.

I would like to thank my other Co-supervisor, Dr Lin Naing, for his patience and tolerance in guiding me in the statistical analysis via online from Brunei. With his guidance and specific coaching, I have learned epidemiology and the skills of analysis, interpretation and reporting, using descriptive statistics, inferential statistics, univariable analysis, multivariable analysis, and binary logistic regression. I wish to also express my gratitude to Dr Kamarul Imran Musa, statistician, for his expert guidance and coaching in developing the 'Risk Prediction Model' and helping me to work out certain statistical issues together with Dr Lin Naing.

I also wish to express my gratitude to Professor Zainul Fadziruddin bin Zainuddin and Professor Syed Mohsin, School of Health Sciences, Universiti Sains Malaysia, for their confidence, specific support, encouragement and giving me leave of absence from work to pursue my postgraduate study.

My sincere thanks to my employer, Universiti Sains Malaysia, for the partial financial support and study leave granted to me to pursue my data collection in Hospital Ipoh and Hospital Terengganu.

I would also like to acknowledge the Head of Department of Microbiology and Parasitology, Universiti Sains Malaysia; Head of Department, Intensive Care Unit, Hospital Ipoh; Head of Department, Intensive Care Unit, Universiti Sains Malaysia; Head of Department Intensive Care Unit, Hospital Terengganu as well as Encik Wan Zainal Azman, Professor Rusli Ismail and Professor Praba Balram including all support staff in the Institute for Research in Molecular Medicine (INFORMM), Health Campus, Universiti Sains Malaysia for their continuous support throughout the study.

Words are inadequate to express my sincere appreciation to all my research subjects (staff and patients); all the staff in Intensive Care Unit, Hospital Ipoh and Universiti Sains Malaysia, for their valuable contribution, time and effort; without which this research could not have been made. I am grateful to the many other concerned staff for appearing as models and for their participation in my video for the intervention program.

I would like to thank Miss Geshina Mat Saat from School of Health Sciences for kindly proof reading my thesis. I am also extremely grateful to the Dean, Professor Ahmad Zakaria, all other working colleagues from the School of Health Sciences as well as School of Medical Sciences, Universiti Sains Malaysia who have contributed directly or indirectly to the successful completion of this research and thesis.

Finally, I would like to express my gratitude to my father, mother, brothers, sisters and my good friend Sooriyakumaran for all their encouragement and emotional support.

TABLE OF CONTENTS

CHAPTER TWO

OVERVIEW OF MATERIALS AND METHODS (PHASE 1, PHASE 2 AND PHASE 3)

CHAPTER THREE

PROSPECTIVE TARGETTED SURVEILLANCE OF NOSOCOMIAL INFECTION IN ADULT MEDICAL-SURGICAL INTENSIVE CARE UNIT (PHASE 1 AND PHASE 3 OF STUDY)

CHAPTER FOUR

KNOWLEDGE ATTITUDE AND PRACTICE IN NOSOCOMIAL INFECTION ICU

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF TABLES

LIST OF FIGURES

LIST OF ABREVIATIONS

AIDS	Acquired immune deficiency syndrome or acquired immunodeficiency syndrome
A & E	Accident and emergency
APACHE III	Acute Physiological and Chronic Health Score
BSI	Blood stream infection
BMI	Basal Mass Index
CA-UTI	Catheter associated urinary tract infection
CR-UTI	Catheter related urinary tract infection
CA-BSI	Catheter associated blood stream infection
CR-BSI	Catheter related blood stream infection
CCU	Coronary Care Unit
CDC	Center Disease Control
CI	Confidence Interval
CVC	Central venous catheter
CPAP	Continuous positive airway pressure
DAI	Device associated infections
E Coli	*Escherichia coli*
ED	Emergency department
ETT	Endotracheal tube
GCS	Glasgow Coma Scale

GIT	Gastrointestinal tract
HAI	Hospital acquired Infection
HCAI	Health care associated infections
HDU	High Dependency Unit
HI	Hospital Ipoh
HUSM	Hospital Universiti Sains Malaysia
HKT	Hospital Kuala Terengganu
IHD	Ischemic Heart Disease
ICU	Intensive care unit
ICUs	Intensive care units
IQR	interquartile range, $Quartile_3 - Quartile_1$
IAC	Intra arterial catheter
IVD	Intravascular devices
IV	intravenous
IVD	Intravascular devices
KAP	Knowledge Attitude Practice
MUAC	Mid upper arm circumference
MVD	Mechanical ventilation devices
NI	Nosocomial Infection
NIs	Nosocomial infections
NNIS	National Nosocomial Infections Surveillance *(*NNIS*)* system

n	sample size, number of data points, or number of trials in a probability experiment
NISDCF	'Nosocomial Infection Surveillance Data Collection Form'
N	Population size
PIVC	Peripheral intravenous catheter
P	Probability value
SAPS II	New Simplified Acute Physiology Score
SD	Standard deviation
SENIC	Study on the Efficacy of Nosocomial Infection Control
SEM	Standard error of the mean
TISS-76	Therapeutic Intervention Scoring System
OT	Operation theater
UTI	Urinary tract infection
UKM	Universiti Kebangsaan Malaysia
USA	United States of America
VAP	Ventilator-associated pneumonia

ABSTRAK

Jangkitan nosokomial (NI) berkaitan peralatan medikal meninggikan kadar mortaliti dan morbiditi (>30%) dan kos perbelanjaan kesihatan. Kajian berkaitan NI amat terhad di Malaysia. Kebanyakkaan kajian adalah kajian retrospektif atau 'point prevalence' Kajian pengetahuan (K), sikap (A) dan praktis (P) di kalangan staf unit rawatan rapi (ICU) tidak dilakukan di Malaysia. Objektif kajian ini ialah (i) mengenalpasti insiden, pola bakteria, jenis NI dan faktor risiko (prediktor) jangkitan berkaitan peralatan medikal; (ii) mengenalpsti kelemahan KAP dalam pencegahan NI di kalangan staf ICU; (iii) membentuk program pencegahan jangkitan NI (iv) menghasilkan dan menilai kalkulator preliminari bagi mengesan jangkitan nosokomial

Kajian ini dilakukan dalam tiga fasa. Fasa pertama ialah kajian Cohort prospektif yang telah dijalankan untuk mengenalpasti insiden dan kepelbagaian jenis jangkitan berkaitan dengan perlalatan (device-related NI) faktor risiko, malpraktis dan pola mikroorganisma dengan menggunakan borang 'Nosocomial Infection Surveillance Form'.di ICU Hospital Ipoh, Hospital Universiti Sains Malaysia and Hospital Kuala Terengganu di Malaysia dari bulan Oktober 2003 sehingga Disember 2006 (n=215). Fasa yang kedua ialah kajian eksperimen (Experimental Study) untuk mengetahui pra-KAP dan Pos KAP di kalangan kakitangan di ICU Hospital Ipoh, (n=38) (kumpulan eksperimen) dan Hospital Universiti Sains Malaysia (n=32) (kumpulan kontrol) dengan menggunakan soal selidik dan permerhatioan. Suatu program intervensi telah diwujudkan berdasarkan hasil pre-KAP dan dinilai keberkesanannya. Fasa tiga ialah kajian sambungan daripada Fasa 1. Analisis 'Survival' ('Simple Cox regression dan Multivariable Cox Proportional Hazard Model') telah diguna untuk mengenalpasti faktor risiko NI iaitu 'ventilator-associated pneumonia'

(VAP), 'catheter-associated urinary tract infection' (CA-UTI) dan 'catheter-associated blood stream infection' (CA-BSI). Kalkulator dibentukkan dengan menggunakan prediktor (faktor risiko) NI dan formula {**HR=*h(t)/ [h0(t)]* = e** $^{(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 \ldots\ldots\ldots B_n x_n)}$**}.**

Keputusan fasa satu menunjukkan NI terjadi selepas 48 jam pendaftaran kemasukan ke ICU (mode 5 hari; purata tempoh penginapan = 10 hari). Kejadian jangkitan ICU berkaitan penggunaan peralatan (ICU-acquired device-related NI) di dalam kumpulan kohort adalah 29.3% *(n*=63). Kadar jangkitan berkaitan peralatan (device-related) VAP adalah 26.5% (n=57) dengan kadar penggunaan alat ventilator mekanikal adalah 88.7%. Kadar CA-BSI adalah 10.7% (n=23) dan kadar penggunaan peralatan intravaskular adalah 95.9%. Jangkitan trek urinari adalah 6% (n=13) dengan kadar penggunnan kateter 96.2%. Kadar kematian termasuk semua jangkitan ICU (ICU-acquired NI) dengan 'sepsis' adalah 6.5%. Insiden VAP dianggap tinggi bagi ketiga-tiga hospital yang dikaji. Dalam kajian ini, organisma dominan adalah *Klebsiella pneumoniae* dalam aspirasi trakeal, darah dan urin. *Acinetobacter* species hanya didapati dalam sekresi trakeal dan darah. Organisma gram positif Methicillin-resistant *Staphylococcus aureus* (MRSA) dikesan dalam darah, aspirasi trakeal dan urin. Kedua-dua kumpulan Gram negatif dan positif didapati dalam kajian ini. Keputusan fasa dua, menunjukkan peningkatan dalam KAP selepas program intervensi (nilai *P* =0.001) dalam kumpulan eksperimen (paired *t*-test: Knowledge-*P*=0.014; Attitude-*P*=0.009 and Practice-*P*=0.001). Perbezaan dalam skor KAP (independent *t*-test) di antara kumpulan kontrol dan eksperimen menunjukkan perubahan yang signifikan (nilai *P* = 0.001). Ini menyokong impak dan kejayaan program intervensi kawalan jangkitan. Dalam fasa tiga, menunjukkan bahawa prediktor untuk

jangkitan VAP adalah 'heavy sedation', 'poor gag reflex', tempoh penggunaan ventilasi mekanikal dan kegunaan pelbagai jenis antibiotik. Setiap satu hari penggunaan ventilasi mekanikal kadar risiko untuk mendapat jangkitan VAP meningkat 6% di tiga hospital yang dikaji. Prediktor CA-BSI adahlah tempuh penggunaan kateter intravena, tempoh penggunaan ventilasi mekanikal, penukaran kateter CVC, kanser dan penggunaan pelbagai jenis antibiotik. Risiko-risiko ini dinyata dan diperkuatkan dalam program intervensi untuk staf semasa kaijan KAP untuk menangani NI di ICU. Prediltor untuk CA-UTI adahlah kadar penggunaan pelbagai jenis antibiotik seharian dan faktor jantina (perempuan). Dalam kajian ini, wanita mempunyai risiko 4.41 kali lebih tinggi untuk dijangkiti CA-UTI berbanding lelaki. Satu percubaan dilakukan untuk menghasilkan kalkulator preliminari bagi mengesan jangkitan nosokomial dengan menggunakan prediktor VAP, CA-BSI dan CA-UTI. Kalkulator ini perlu dikaji dan dinilai dengan lebih mendalam. Kajian insiden ini adalah kali pertama dijalankan di Malaysia. Prediktor yang dikenalpasti dalam kajian ini akan meyedarkan staf ICU tentang risiko meningkatnya NI dari aspek penggunaan peralatan medikal. Program intervensi menunjukkan bahawa NI berkaitan peralatan boleh dikurangkan. Penemuan ini akan memberi kesan terhadap amalan kawalan jangkitan di tiga hospital juga lain-lain hospital di Malaysia. Sumbangan besar kajian ini adalah ia boleh mengurangkan risiko NI, mortaliti dan morbiditi serta pengurangan dalam kos penjagaan kesihatan di hospital.

ABSTRACT

Device-associated nosocomial infection (NI) increases the mortality and morbidity rate (>30%) and healthcare costs. Studies on NI were limited in Malaysia. Most studies were retrospective or on point prevalence. Gap in Knowledge (K), Attitude (A), Practice (P) studies on prevention of ICU-acquired NIs were not available in Malaysia. The objectives of the study were to (i) identify the incidence, bacterial patterns and predictors of device-associated NI, (ii) to identify the gap in KAP in infection control practices related to device-associated nosocomial infections, (iii) to develop and evaluate an intervention program and (iv) to develop a preliminary bed-side calculator to detect NI. This study was done in three phases. Phase 1 was a three-year prospective Cohort observation study conducted on the incidences and different types of device-associated NI, risk factors, adverse healthcare practices and patterns of the microorganisms isolated on patients (*n*=215) in ICUs of Hospital Ipoh, Hospital Universiti Sains Malaysia and Hospital Kuala Terengganu in Malaysia from October 2003 to December 2006 using a developed 'Nosocomial Infection Surveillance Form'. Phase 2 was an experimental study conducted to elicit the pre-KAP and post-KAP data of staff using questionnaire and observation in both the experimental (Hospital Ipoh) (*n*=38) and Control Group (Hospital Universiti Sains Malaysia) (*n*=32). An intervention program was developed based on Pre-KAP results and evaluated for its effectiveness. Phase 3 was a continuation of data collection from Phase 1 to identify predictors of ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CA-UTI) and catheter-associated blood stream infection (CA-BSI) using survival analysis (simple Cox regression and multivariable Cox proportional hazard model). A preliminary 'bed-side calculator was developed using the

predictors using the formula {**HR=*h(t)/ [h0(t)]* = e** $^{(\beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \beta_5 x_5 \ldots\ldots\ldots B_n x_n)}$**}.** Results from phase 1 showed that NI occurred after 48 hours post admission (mode=5 days; mean=10 days). The incidence of ICU-acquired device-related NI in the cohort group was 29.3 % (*n* = 63). Device-associated VAP was 26.5 % (*n*=57) with a mechanical ventilator utilization rate of 88.7%. CA-BSI was found to be 10.7% (*n*=23) with intravascular devices utilization rate of 95.9% while CA-UTI was 6% (*n*=13) with a catheter utilization rate of 96.2%. The death rate due to all ICU-acquired NI including sepsis was 6.5%. The incidence of VAP was considered high for the three hospitals studied. In the current study, a predominance of *Klebseilla pneumoniae* was observed in tracheal aspirate, blood and urine whereas *Acinetobacter* species was isolated only from tracheal aspirate and blood. The Gram positive organism Methicillin-resistant *Staphylococcus aureus* (MRSA*)* was isolated from blood, tracheal aspirate and urine. Result in phase 2 showed that there was an improvement in KAP after intervention program on 'Prevention and Control of Device-associated NI' in the experiment group (paired *t*-test: Knowledge-*P*=0.014; Attitude-*P*=0.009 and Practice-*P*=0.001). Independent *t*-test showed that there was an improvement in KAP in the experimental group in comparison to the control group (*P*=0.001). The developed intervention program with specific infection control strategies for ICU-acquired device-associated NI was effective in the experimental group. Furthermore, the differences in KAP scores between experimental and control group showed a significant change which highlighted the impact and success of the infection control intervention program. In phase 3 the predictors for VAP were heavy sedation (poor gag reflex), duration of mechanical ventilation and number of multiple antibiotics. Every one day increase in the usage of

mechanical ventilation increased the risk of getting VAP by 6% in the three hospitals studied. The predictors identified for CA-BSI were 'duration of infusion' given via central venous catheter (CVC), 'duration of mechanical ventilation', 'changing of central venous catheter' during ICU stay, 'cancer' and 'number of multiple antibiotics'. The predictors for CA-UTI were 'gender (female)' and 'number of multiple antibiotics'. In this study, females were 4.41 times at increased risk of acquiring CA-UTIs then the males. These risks were highlighted and reinforced in the prevention of NI in ICU in the intervention program for staff during the KAP study. In conclusion, this is the first incidence study in Malaysia on ICU-acquired device-associated NI related to the usage of medical devices in ICU. The predictors identified in this study and the developed bedside-calculator will alert the ICU staff in advance for possible risk of development of device-associated NI. An intervention program implemented on the experimental group showed that ICU-acquired could be reduced. These findings will impact the infection control practices in the three hospitals and other hospitals in Malaysia. A preliminary bedside calculator need to be further studied and evaluated. The biggest contribution of the study is that it can reduce NI, mortality and morbidity and indirectly reduce the costs of healthcare.

CHAPTER ONE

INTRODUCTION

LITERATURE REVIEW

1.1 Nosocomial infections in intensive care units (ICU)

Nosocomial infection (NI) is a term derived from the Greek word *nosos* for 'disease'. ‘Nosocomium’ in Latin means ‘hospital’. ‘Nosocomium’ in Greek means ‘one who tends to the sick and alleviates suffering’ (Tortora et al., 1994). According to Castle and Ajemian (1987), the term ‘nosocomial’ means ‘bed associated’ and the word ‘infection’ has been defined as the ‘process whereby pathogenic organisms become established and multiply in or on the body of the host’ Therefore, the infections that occur in hospitals are called ‘Nosocomial Infections.’ Currently, NI is also known as Hospital acquired infection (HAI) or Healthcare-associated nosocomial infection (HCAI).

Nosocomial infection (NI) is a worldwide problem. National studies on prevalence of NI in developed countries report it to be approximately 10% (Ayliffe et al., 1999; Asefzadeh, 2005). The majority of research studies on NIs are from the western world (Rosenthal et al., 2006). Relatively little data have been reported from Malaysia (Tan, 1998), especially regarding rates related to device-associated NI using standardized Centre for Disease Control and Prevention (CDC) (1994) definitions or Study of Efficacy of Nosocomial Infection Control (SENIC).

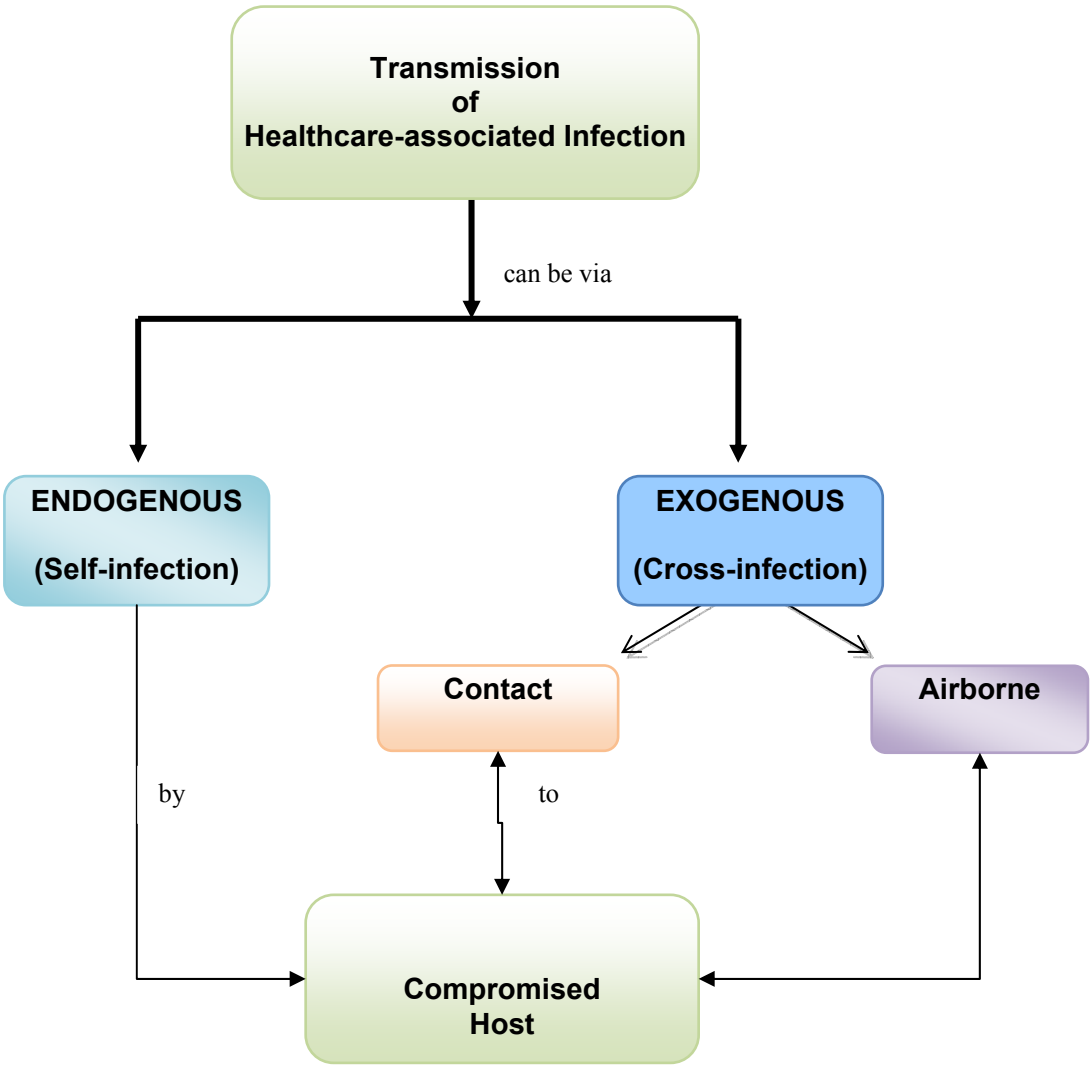
The incidence of NI in Intensive care units (ICU) is usually higher than wards in the hospital (Trilla, 1994 and Ylipalosaari et al., 2006 [a,b]). About one in ten patient acquires an infection as a direct result of being hospitalized. Universally more than 20% of patients in ICUs are at risk of NI (Orsi, 2006). Nosocomial infection is highly associated with a significant morbidity and mortality rate (>30%) of patients in ICU (Tan, 1998; Orsi, 2006). The vital elements contributing to NI are the source of infectious agent, susceptible host and mode of transmission (Stucke, 1994; Smith & Rusnak, 1997[a,b]). The sources of infectious agent include the skin scales from bed linen and dressing, droplets, wounds, nebulizers, humidifiers, dust from floors, street, building, shelves, corridors and fans. The transmission of NI occurs when precautions are not taken to prevent transmission of microorganisms for example incorrect hand washing techniques, break in asepsis during invasive procedures, incorrect usage of personal protective equipments during invasive procedure and when providing care to critically ill patients who are the compromised host.

Modernization of ICUs and hospitals as complex institutions in the 1990's with administration of a variety of antibiotics and a variety of new diagnostic and therapeutic services (as cited by Wenzel, 1997) have corrupted the goal of caring and healing. Hospitals have become a place used as tools for better diagnosis and are no longer a place for relief of infections (Trilla, 1994; Perry, 1998; Russell, 1998; Schmid, 2001). The development of these infections are not only attributed to the causative micro organisms but are influenced by multiple factors. ICU's are now considered as culture media for newer strains of bacteria and enhancing resistance to multiple antibiotics. One of the causes is the lack of attention to infection control practices and procedures (Russell, 1998) related to the usage of mechanical

ventilation devices, urinary catheters and intravenous catheters. The break in infection control practices include omission of hand washing or incorrect hand washing technique, incorrect gloving techniques, misuse of personal protective equipments, break in asepsis when carrying out invasive procedures and providing nursing care (Trilla, 1994; Perry, 1998; Russell, 1998; Schmid, 2001; Orsi, 2006). These factors have contributed to longer stay in hospitals, increased cost and an increase in NIs in ICUs. Therefore, the risk of acquiring NI is higher among patients who stay longer in ICUs (Trilla, 1994; Fernandez-Crehuet et al, 1997).

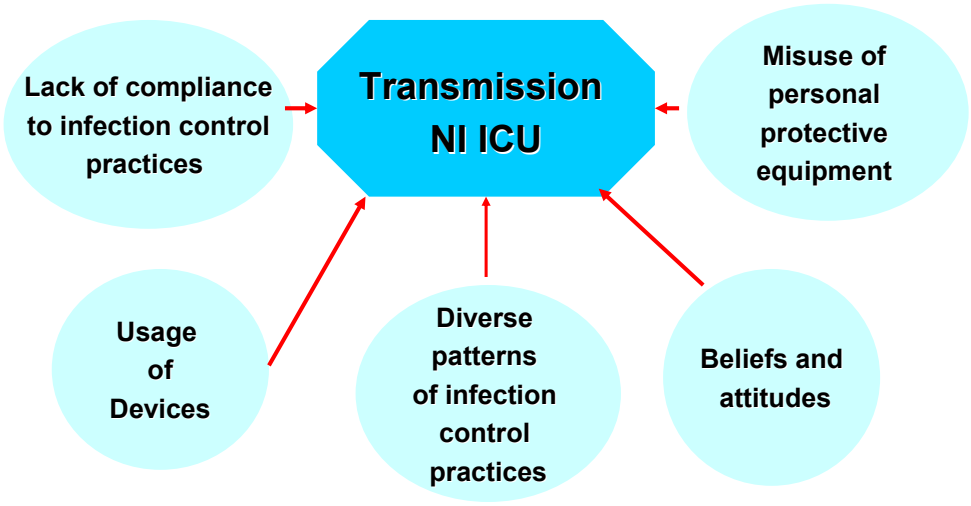
Various reports, globally, have also shown that good surveillance practices, shorter duration in usage of medical devices, and a good intervention program with frequent continuous re-enforcement would decrease the overall rate of infection in ICU (Velasco, et al., 1997; Perry, 1998; Russell, 1998; Schmid, 2001; Orsi, 2006; Rosenthal et al., 2004[a,b]; Ylipalosaari, P. et. al., 2006 [a,b]; 2007[a,b]).

Nosocomial infections often become apparent while the patient is still in hospital, but in some cases the symptoms may not occur until the patient is discharged from the hospital. In summary, NI, HAI or HCAI occurs when an organism is transmitted via direct contact or airborne to a patient or staff, the hospital environment or equipment (Stucke, 1994; Smith & Rusnak, 1997[a,b]). Nosocomial infection normally becomes evident between 48 hours to 72 hours after admission (Stucke, 1994; Smith & Rusnak, 1997[a,b]; Fernandez-Crehuet et al, 1997; Richards et al., 2000). The sources, reservoir and mode of transmission of HCAI are as shown in Figure 1.1-1.4. Table 1 shows the normal floras in the human body which can become potential pathogens in a compromised host.



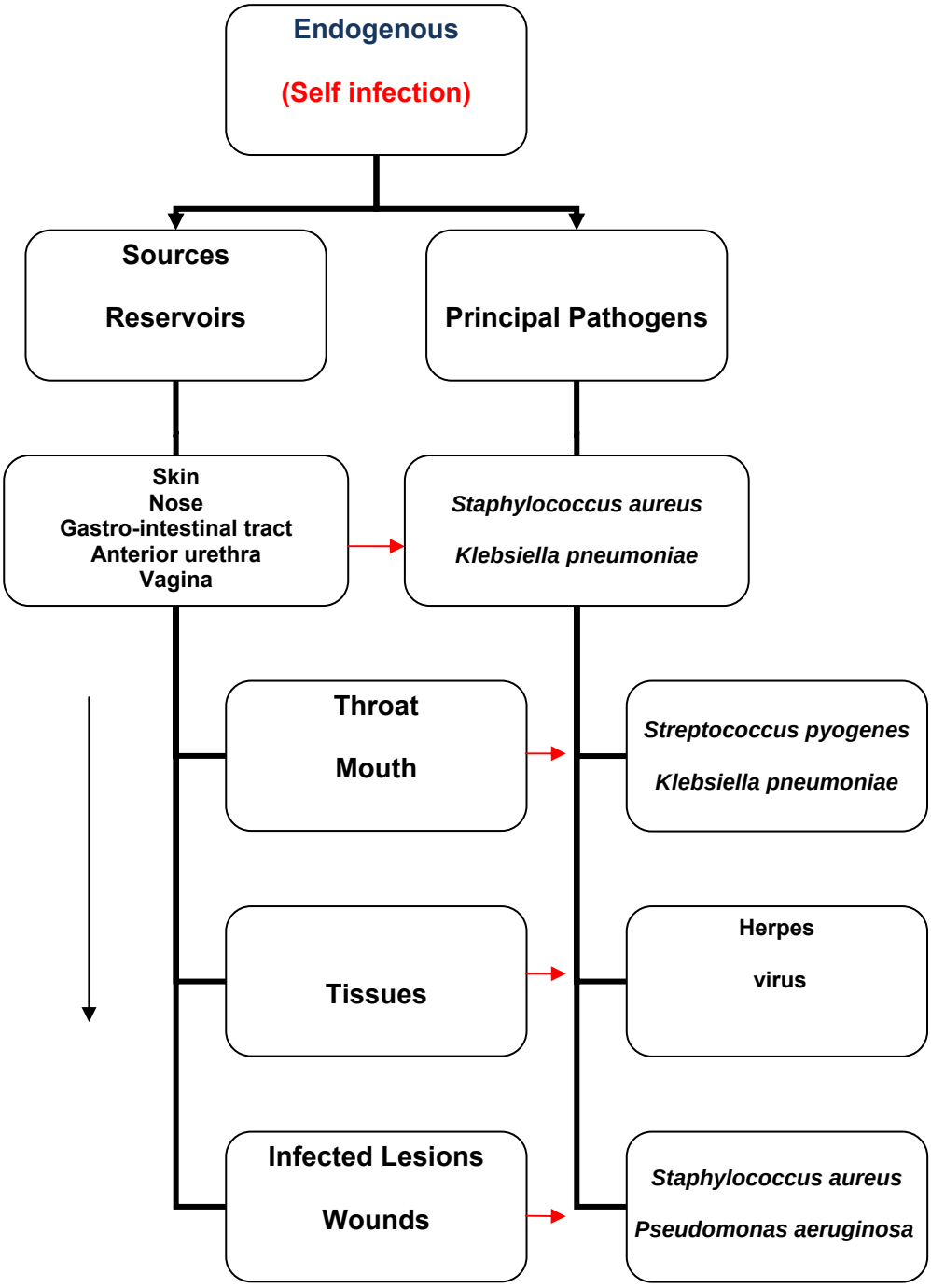
(Diagram prepared from data in Ylipalosaari et al., 2006 [a,b]; Mayhall,1999; Wenzel, 1997, pp. 822-832; Wenzel & Wenzel, 1983; Weinstein, 1991; Tortora et al., 1994; Castle & Ajemian, 1987 and Lowbury et al., 1981)

Figure 1.1: Transmission of Healthcare-associated Infection



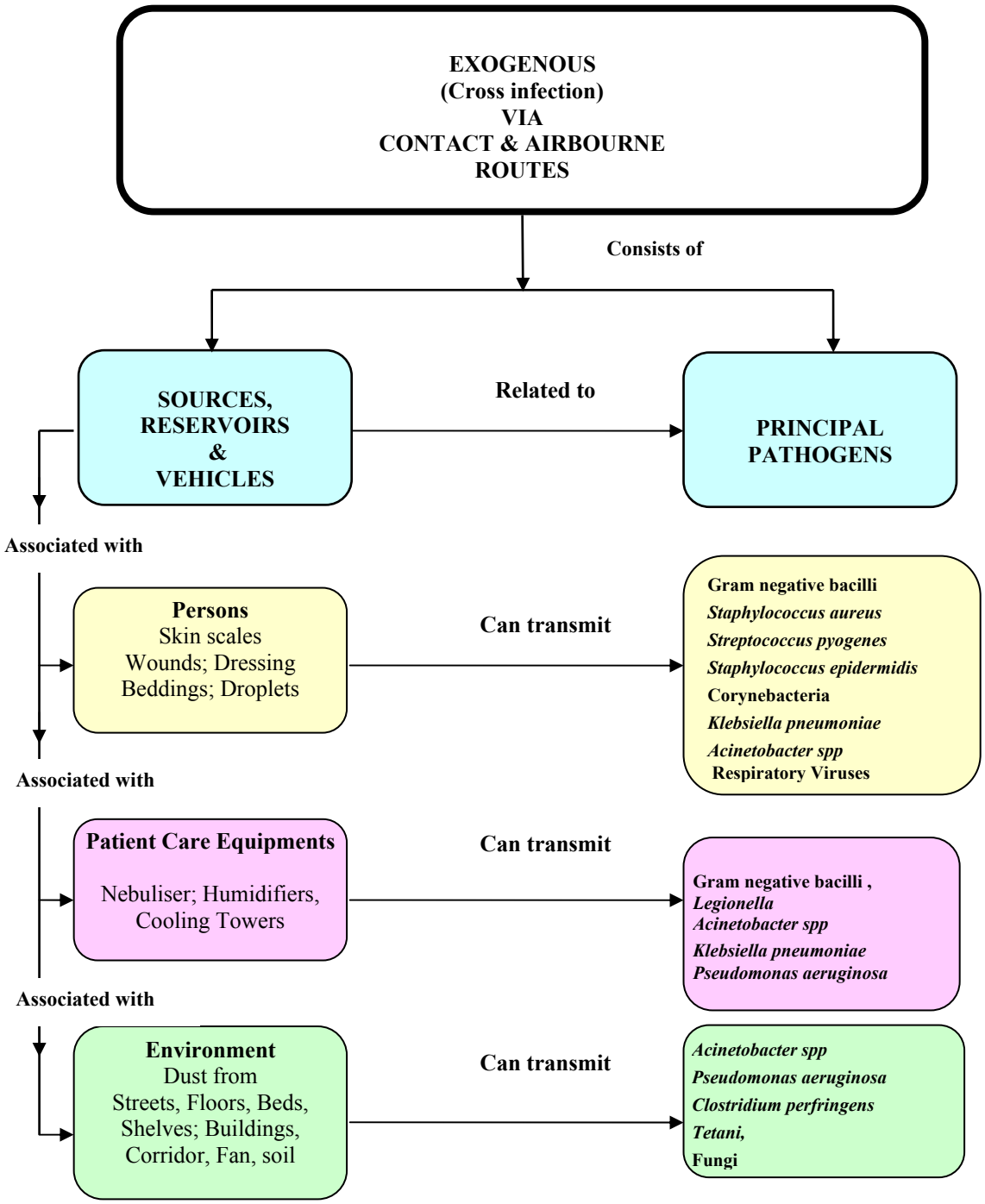
(Diagram prepared from data in Ylipalosaari et al.,2007[a]; Ylipalosaari,2007; Ylipalosaari et al.,2006 [a,b]; Vincent et al.,2006; Agarval et al.,2006; Torres, 2006; Torres et. al.,1999; Wenzel,1997, pp. 822-832; Velasco et al.,1997; Fernandez-Crehuet, et al.,1997; Weinstein, 1991; Tortora et al.,1994; Tortora et al.,1989; Castle & Ajemian,1987; Lowbury et al.,1981)

Figure 1.2: Chain of Transmission of Infection in ICU



(Diagram prepared from data in Wenzel, 1997, pp. 822-832; Tortora et al., 1994; Tortora et al., 1989; Castle & Ajemian, 1987; Lowbury et al., 1981)

Figure 1.3: Endogenous Self- infection in Compromised Host



(Diagram prepared from data in Castle and Ajemian, 1987; Lowbury et al., 1981; Tortora et al., 1994; Wenzel, 1997, pg 810-815)

Figure 1.4: Exogenous Cross Infection-Vehicles of Infection and Principal Pathogens

Table 1 Normal Flora found in the Human Body

BACTERIA	Skin	Eye	Nose	Pharynx	Mouth	Lower GIT	Anterior. urethra	Vagina
Staphylococcus epidermidis (1)	++	+	++	++	++	+	++	++
*Staphylococcus aureus** (2)	+	+	+	+	+	++	+	+
Streptococcus mitis				+	++	+	+	+
Streptococcus salivarius				++	++			
*Streptococcus mutans** (3)				+	++			
*Enterococcus faecalis** (4)				+	+	++	+	+
*Streptococcus pneumoniae** (5)		+	+	+	+			+
*Streptococcus pyogenes** (6)	+	+		+	+	+		+
Neisseria sp. (7)		+	+	++	+		+	+
*Neisseria meningitidis** (8)			+	++	+			+
Enterobacteriaceae**(Escherichia coli)* (9)		+	+	+	+	++	+	+
Proteus sp.		+	+	+	+	+	+	+
*Pseudomonas aeruginosa** (10)				+	+	+	+	
Klebsiella pneumoniae	+				+	+		
*Haemophilus influenzae** (11)		+	+	+	+			
*Bacteroides sp.**						++	+	+
Bifidobacterium bifidum (12)						++		
Lactobacillus sp. (13)				+	++	++		++
*Clostridium sp.** (14)					+	++		
Clostridium tetani (15)						+		
Corynebacteria (16)	++	+	++	+	+	+	+	+
Mycobacteria	+		+	+		+	+	
Actinomycetes				+	+			
Spirochetes				+	++	++		
Mycoplasmas				+	+	+	+	+

GIT- gastrointestinal tract; + = present; * potential pathogens

(Adapted from Todar,2004, http://www.textbookofbacteriology.ne;Tortora et al., 1989; 1994)

1.2 Historical perspectives and the present day impact of nosocomial infection in intensive care units

1.2.1 Condition in the Era of 1750-1950

The literature on control of infections in hospitals has been cited since the mid 1700's (Wenzel, 1997). Nosocomial infection can be traced back to the first hospital, Hotel Dieu near the Seine River which was built in Paris in the 7th century (Castle & Ajemian, 1987; Wenzel, 1997). The conditions in Hotel Dieu were very primitive with up to eight (8) patients sharing a bed, no heating system and no nutritious food (Castle & Ajemian, 1987; Wenzel, 1997).

Patients' wounds were washed daily with the same wash cloth or sponge. This caused wound infection in all patients. Mortality was about 60% (Castle & Ajemian, 1987). The maternity wards were located in the basement of the hospital. During floods, the ward was flooded by the river with garbage which led to puerperal fever killing 20 women in an epidemic, in 1765 (Castle & Ajemian, 1987; Wenzel, 1997). Poor hygiene and sanitary conditions, poor diet and cold temperatures increased the rate of infections (Castle & Ajemian, 1987, Wenzel, 1997).

1.2.2 Link between bacteria and infection and introduction of aseptic techniques

Back in the 1840's and the 19th century, puerperal sepsis or fever was a fatal disease in Europe. Oliver Wendell Holmes, Ignaz Philipp Semmelweis, Joseph Lister and Florence Nightingale (Wenzel, 1997) played major roles in reducing this infection. Semmelwei, while working in Vienna General Hospital was concerned about the death of women with puerperal fever (Wenzel, 1997). Semmelweis also demonstrated

that hand washing was important in preventing and reducing the mortality for puerperal sepsis (Wenzel, 1997) and also emphasized that overcrowding was not the cause of puerperal fever. Holmes had reported that physicians who did autopsies followed by an examination of women in labour were transmitting disease from the autopsied body to the maternity patients through clinical observation (Wenzel, 1997). Both Semmelweis and Holmes were not aware that bacteria were transmitted from staff to patient and from patient to patient (Wenzel, 1997).

Joseph Lister was first to demonstrate the link between bacteria and infection (Wenzel, 1997). Lister recognized the risk of microbial infection transmissions to instruments and fingers. Lister further stated that infection could be prevented by killing the organisms in the wound and by preventing contaminated air from coming in contact with these wounds. He first developed the concept of asepsis (Wenzel, 1997).

Florence Nightingale in 1860 initiated the aseptic techniques into practice. She was adamant for hand washing, wearing of gloves, isolation procedures for infected patients, good ventilation and good sanitation which formed the basis for infection control programs. Infection mortality and morbidity were lowered with the application of such aseptic techniques.

The Manchester Infirmary in 1771 made sure that all patients had clean sheets on the day of admission. The sheets were changed once in three weeks and each patient had his/her own bed (Wenzel, 1997). Patients with infections were segregated. Britain

formalized segregation of patients with fever and small pox in the early 19th century (Castle & Ajemian, 1987; Wenzel, 1997).

Lister's data showed that in 1864-1866 (that is before the introduction of antiseptic methods), mortality rate after amputation was 46% but in the year 1867-1869 (that is after the introduction of antiseptic method), the mortality rate of amputation dropped to 15% (Wenzel, 1997).

Data as an outcome of segregation practices were collected, but the statistical results were fragmented and hence were not applicable. An attempt was made to measure the nosocomial spread of typhus in the London Fever Hospital. Of the 1080 typhus cases, only 27 patients suffered nosocomial infection and eight died (Castle & Ajemian, 1987). The nosocomial spread of typhus in the general ward occurred in one of every four cases admitted to the London Fever Hospital (272 cases admitted, 71 cases had nosocomial infection, 21 died).

Nightingale and Farr, using statistical analysis to study mortality and morbidity rate in soldiers in 1856, observed a significant reduction in deaths after the implementation of improved hygiene practices and a standardized reporting system (Wenzel, 1997). Nightingale developed a system of collecting observational data for analysis of calculating mortality rates (Wenzel, 1997).

1.2.3 19th century and introduction of sterilization

In 1910, the use of sterile equipments, gloves, masks and gowns were a standard protocol in large hospitals (Wenzel, 1997). From antisepsis, asepsis was practiced by killing bacteria with heat. This made a great impact on surgical procedures and the eradication of wound infections (Wenzel, 1997). In 1933, Meleney, a surgeon as well as a bacteriologist (Wenzel, 1997) investigated epidemics of wound infection with staphylococcal and streptococcal species. Other hospital acquired infections were totally ignored. In the study, wound infection dropped from 14% to 4.8% (Wenzel, 1997).

1.2.4 Quantitative measure of infection and urinary catheter associated infection

In 1929, Cuthbert Dukes discovered asymptomatic bacteriuria and urinary tract infection in patients who had rectal surgery (Wenzel, 1997). Dukes developed a quantitative measure for infection in the urinary tract based on the number of leukocytes in the urine. He showed that less than 10 leukocytes/ml was normal and greater than 100 leukocytes/ml suggested infection until proven by a positive culture. Observing the patients on a daily basis, he noticed that the urine was sterile until the second or third day amongst patients with urinary catheters. After the third day, S*taphylococci* or *coliforms* were isolated. By sixth to eighth day, there was a marked increase in leucocytes between 100 to 1000 cells per ml of urine (Wenzel, 1997).

1.2.5 Antibiotic era and decline in aseptic techniques

The antibiotic era began in 1940 after the discovery of chemotherapeutic properties of penicillin by Dr. Howard Florey and Sir Ernest Chain in Great Britain (Castle & Ajemian, 1987). Sir Florey and Sir Chain were able to demonstrate that penicillin has unique chemotherapeutic properties: minimal toxicity to animal tissues and an antibacterial activity far greater than that of other drugs (Castle & Ajemian, 1987) as a result, penicillin became available in 1941 to treat military causalities during World War II for pneumonia, blood poisoning, scarlet fever, syphilis, gonorrhea and rheumatic fever. The death rate showed a remarkable reduction from 18% to 1% (Castle & Ajemian, 1987).

The discoveries of new drugs (e.g. penicillin) led however, to its indiscriminate use. This resulted in the emergence of resistant strains, change in microbial flora and continued occurrence of infections (Castle & Ajemian, 1987). There was also a decline in aseptic techniques (Castle & Ajemian, 1987) with importance given to antibiotics instead.

1.2.6 Emergence of infection control as a discipline and formation of Committee for Infection Control

In the 1950's there was a drastic increase in *Staphylococcal* infections and resistance to penicillin. A Committee for Infection Control was formed in 1958 by the American Hospital Association with multidisciplinary members to reduce infection (Castle & Ajemian, 1987). An Infection Control Practitioner (ICP) was identified based on Nightingale's ideology. The committee was responsible for developing and analyzing infection control protocols and antibiotic therapy. The first Infection Control Sister

(ICP) was appointed in 1959 at Torbay Hospital in England (Castle & Ajemian, 1987). She liaised with all personnel and disciplines in the hospital in relation to asepsis. In United States, Kathryn Wenzel, a nurse, was appointed as an ICP in 1963 at the Stanford University Medical Center (Castle & Ajemian, 1987).

The ICP must have good knowledge of hospital skills and services, experience in nursing, microbiology, infectious disease, epidemiology, administration and supervision, law and ethics, public health and environmental sciences with a Master's degree (American Hospital Association, 1979; Castle & Ajemian, 1987, Wenzel, 1997). ICP was a free agent in the hospital unhindered by administration in investigating, implementing, recommending and enforcing control measures (Castle & Ajemian, 1987). With the above measures in place, the rate of nosocomial infection reduced. The risk groups changed and the microorganisms causing infection also changed, despite the ongoing review of infection control guidelines.

With the emergence of Infection Control as a discipline and appropriate use of antibiotics, nosocomial infections were effectively controlled. The Center for Disease Control (CDC) developed guidelines to provide control measures and designed programs to monitor nosocomial infections (American Hospital Association, 1979).

1.2.7 Lawsuits related to nosocomial infection with the moral obligations

In 1965 health care workers were further pressurized with the possibility of lawsuits related to nosocomial infection with the moral slogan of 'to do no harm to patients' by regulatory agencies of health care workers. This gave added importance to infection control in hospitals (Castle & Ajemian, 1987).

1.2.8 Intensive care units identified as high risk areas for nosocomial infection

The ICUs were identified as high risk areas for the development of nosocomial infection. The rationale was that the patients were severely compromised, required close observation and nursing care with a variety of therapies using drugs or equipments. Compared to other disciplines, the distribution of infection in ICU differs widely because NIs are associated with severity of illness, prolong stay, the individual usage of equipments like mechanical ventilation (ventilator-associated pneumonia), indwelling urinary catheter drainage (catheter-associated urinary tract infections), intravenous and intra-arterial catheters (catheter-associated blood stream infections) and surgical procedures (nosocomial surgical wound infection) on ICU patients (Trilla, 1994; Fernandez-Crehuet et al., 1997; Richards et al., 2000; Rosenthal et al., 2003[a]; Rosenthal et al., 2003[b]). In addition, patients as host become colonized with virulent or resistant microorganisms. The physical closed structure of the ICU and poor ventilation allows for the easy transmission of pathogens (Wenzel, 1997).

In conclusion, the most confounding factor that determines ICU as a high risk area is the length of stay, severity of illness and the period of exposure to the use of the invasive devices on the severely compromised patient (Trilla, 1994; Frenandez-Crehuet et al., 1997; Richards et al., 2000; Rosenthal et al., 2003[a,b]).

1.2.9 Malaysian historical perspectives related to control of nosocomial infections

In Malaysia, very little has been published about historical perspectives and infection control issues in hospitals attached to the Ministry of Health, as well as in hospitals attached to the Universities and the private sector. The annual reports of the hospitals

were not easily accessible. In certain situations, approval from the Ministry of Health is required before it can be quoted in any write up because of confidentiality issues.

In University Malaya Medical Center, a 900 bedded university hospital, the nosocomial infection, and infectious disease surveillance were conducted by the Infection Control Unit in the Department of Medical Microbiology since the early seventies in Malaysia (Annual Report, University Malaya Medical Center, 2004). A staff nurse under the guidance of a Medical Microbiologist assisted in all types of infection control activities. In the year 2000, an infection control sister was appointed to cope with the increasing workload related to nosocomial infections in all Ministry of Health Hospitals (Annual Report, Hospital Ipoh, 2002).

1.2.10 First unit for nosocomial infection

In Malaysia, in the year 2000, the first separate unit for nosocomial infection was established in the Ministry of Health with an experienced matron in charge, thereby NI became a specialty with special focus (Annual Report, Hospital Ipoh, 2002). At that time, all the 13 hospitals under the Ministry of Health had for the first time a NI control unit with a sister-in-charge and staff nurses to monitor in the various disciplines. The aim was a focused surveillance and monitoring for NI under supervision of a medical doctor in the hospitals, mainly focusing on critical care areas (Annual Report, Hospital Ipoh, 2002).

Yearly reports with raw data are still being compiled, and disseminated to the Ministry of Health. Guidelines are continuously updated. The first nosocomial infection control unit in the University Malaya Medical Center was formed on 3rd

April 2000, under the direction of the Hospital Director and Chairman of the Infection Control Committee, Prof. Dato' Dr. Anuar Zaini Mohd. Zain (Annual Report, 2004).

1.2.11 Training

Staffs were normally trained in-house. Universiti Kebangsaan Malaysia had played an active role in running various workshops on Infection Control for Malaysia by inviting speakers from Hong Kong, Singapore and Malaysia. The Malaysian Society of Infectious Diseases and Chemotherapy and the Infectious Control Association of Malaysia were also established to update the knowledge of health care workers in infectious infection control practices since before 2003. Experts from Hong Kong, Australia and other countries were invited to share their expertise and knowledge. Training courses on Infection Control were also carried out by the Institute for Medical Research (IMR), Kuala Lumpur in March 2003 and by the Association of Private Hospital in Malaysia for infection control personnel (Annual Report, 2003), Association of Private Hospitals of Malaysia.

1.3 Epidemiology of nosocomial infection in intensive care unit

Epidemiology can be defined as a scientific study on the 'transmission, incidence, and frequency of disease' (Tortora et al., 1989, 374; Tortora et al., 1994). It is the "study of distribution and determinants of disease frequency in human population" (Trilla, 1994, 1-4). This definition clarifies the meaning of epidemiology by highlighting that human beings do not contract diseases randomly and thereby "a disease has both a causal and preventative factor" (Trilla, 1994, 1-4).

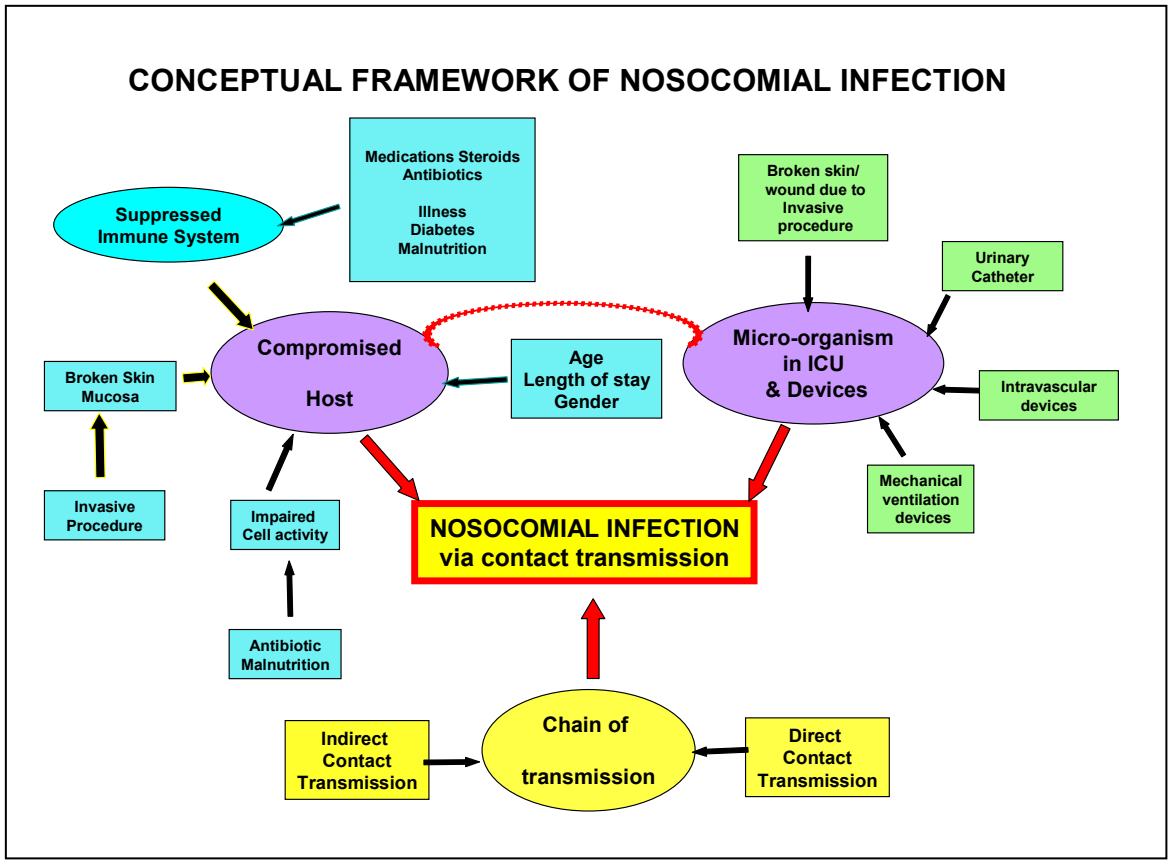
Prevalence and incidence are integral in examining epidemiology of NI in ICUs. "Prevalence" is defined as the proportion of patients in ICU with infections at a given point of time. In other words, it determines the magnitude and characteristics of infection at a given point of time (Castle & Ajemian, 1987). In prevalence analysis, data collection is less time consuming because patients are visited on a single occasion only and the presence of infection, if any is recorded.

"Incidence" is defined as the number of new cases in a defined population over a defined period of time to a targeted unit (Ayliffe et al., 1999). In incidence analysis, continuous surveillance of the patient or unit is observed daily and laboratory results are examined for presence of infection over a given period of time (Ayliffe et al., 1999).

Many records of observations are available. It is very time consuming but the epidemiological evidence gives an in depth basis for rational control measures. The American Hospital Association (1979) defined incidence of NI as "The frequency of occurrence of NI over a period of time and in relation to the population in which it occurs and is expressed as rates".

ICU acquired nosocomial infection is defined as the infection acquired during ICU stay (Tortora et al., 1994). Patients admitted to ICU are five to ten times more likely to get NI compared to other hospitalized patients (Schmid, 2001). In fact, NI accounts for approximately 25% of all hospital infections (Trilla, 1994).

ICU NI is the outcome of the interaction of three principal factors which are (i) the microorganisms in the ICU (hospital environment); (ii) the compromised or critically ill host; and (iii) the chain of transmission in ICU (hospital) (Tortora et al., 1994) as shown in figure 1.1- 1.4. It is postulated that no one single principle factor can cause NI. This is further illustrated in Figure 1.5 as follows.



(Diagram drawn from information in Broaddus & Fu, 2008; Cagatay et al., 2007; Agarwal et al., 2006; Asefzadeh, 2005; Ayliffe et al., 1999; Wenzel, 1997, pp.750-753,.783-792; Trilla, 1994)

Figure 1.5: Contributing Factors of Nosocomial Infection in ICU

(i) Microorganisms

NI can be caused by both Gram positive and Gram negative bacteria, fungus and viruses. The main microbes involved in NI are Enterobacteriaceae (*Escherichia coli, Klebsiella* species*, Proteus species and Serratia marcescens*); *Staphylococcus aureus;* Enterococci and *Pseudomonas aeruginosa.*

Inappropriate usage of antibiotics causes antibiotic resistance strains. Antibiotic-resistant strains are a threat because these resistant strains will become part of the flora of the patient and staff in the ICU or environment of the hospital (Tortora et al., 1994; Wenzel, 1997). A normal level of host resistance is refractory to infections. The patients in ICU being immuno-compromised have a higher susceptibility to being infected by these strains.

(ii) Compromised host

A compromised host is a patient whose resistance is impaired by the disease process (diabetes, leukemia, burns, kidney disease, and malnutrition) or therapy (steroids/radiation) or who is critically ill. Three principles that compromise the patient (host) are broken skin or mucosa, suppressed immune system and impaired cell immunity (activity-response of effector cells such as phagocytes, T-lymphocytes and B-lymphocytes). Body conditions that alter the action of these effector cells are malnutrition, cirrhosis of the liver, and a number of diseases or therapy conditions. B-lymphocytes (white blood cells) develop into antibody producing cells to provide humoral immunity.

(iii) Chain of transmission

Some of the most important routes of transmission of NI are from direct contact from staff to patient, from equipment to patient, and from patient to patient. Certain diagnostic and invasive procedures provide a formite route for many different types of NIs such as catheterization, intravenous therapy, and intubation.

1.3.1 Risk factors and Types of Nosocomial Infection

ICU infections are associated with multiple risk factors interacting with patients' state of health. Tables 1.1, 1.2 and 1.3 illustrate various specific risk factors for the three main types of device-associated nosocomial infection in ICUs.

Table 1.1: Risk Factors for Catheter-associated Blood Stream Infections

Host Conditions	Microbial Factors	Therapeutic Factors	Environmental
1. Extreme Age	Type of Microorganism (virulence) *Gram negative* *Gram positive* *Fungal* *Coagulase –negative staphylococci*	Length of ICU stay	Exogenous factors
2. Pre-existing Co- Morbids *Burn patients*	Bacterial inoculum	Length of hospital stay prior to admission into ICU	ICU environment
3. Underlying disease	Process of host colonization	Indwelling devices or intravascular catheters *Central venous lines* *Arterial lines* *Multiple stop cocks* *Site of catheter*	Insufficient Nurse to patient ratio *Inadequate catheter care* *Care of hub dressing*
4. Severity of Illness	Antimicrobial resistance	Invasive procedures (number)	Adherence to asepsis practice
5. Nutritional Status *Malnutrition (BMI)* *Obesity*	*Serum albumin level* *Body Mass Index*	Adequacy of therapy for primary infection	

(Table prepared from data of Lowbury et al., 1981; Castle & Ajemian, 1987; Tortora et al., 1994; Wenzel, 1997, pp.822-832, Trilla, 1994; Fernandez-Crehuet et al, 1997 Agarwal et al,2006)

Table 1.2: Risk Factors for Ventilator-associated Pneumonia

Host Conditions	Microbiology Factors	Therapeutic Factors	Environmental
1. Extreme Age	Type of Microorganism (virulence) *Acinetobacter species* *Pseudomonas species* *Staphylococcus aureus*	Duration of ICU stay	Exogenous factors
2. Pre-existing Co- Morbids	Bacterial inoculum	Length of hospital stay prior to admission into ICU	ICU environment
3. Underlying disease *Chronic obstructive pulmonary disease* *Neuromuscular disease* *Surgery to thorax or Upper abdomen* *Trauma to head and Chest*	Process of host colonization	Ventilation Intervention *Indwelling devices or catheters* *Nasogastric tube* *Duration of Endotracheal intubation* *Duration of Mechanical Ventilation* *Humidification*	Nurse patient ratio Adequacy of Nursing Care *Adherence to asepsis practice* *Suctioning technique and Frequency* *Postural Drainage Physiotherapy* *Frequent Oral care*
4. Severity of Illness *APACHE Scoring* *SAPS II Scoring* *TISS Scoring*	Antimicrobial resistance	Invasive procedures *Chest tube* *Tracheostomy*	
5. Nutritional status *Obesity* *Poor nutrition*		Adequacy of therapy for primary infection	
6. Decreased consciousness *Impaired airway reflexes* *Aspiration*		Positioning *Frequent change of Body positions* *Elevation of head and chest* Stress Ulcer Prophylaxis *Antacids /H2 Blockers/ Sucralfate*	

Key: APACHE III= Acute Physiological and Chronic Health; SAPS II=New Simplified Acute Physiology Score; TISS=Therapeutic Intervention Scoring System

(Table prepared from data of Lowbury et al., 1981; Castle & Ajemian, 1987; Tortora et al., 1994; Wenzel, 1997, pp.822-832, Trilla, 1994; Fernandez-Crehuet et al, 1997 Agarwal et al,2006)

Table 1.3: Risk Factors for Catheter-associated Urinary Tract Infections

Host Conditions	Microbiology Factors	Therapeutic Factors	Environmental
1. Extreme Age	**Type of Microorganism (virulence)**	Length of ICU stay	Exogenous factors
	Escherichia coli *Pseudomonas aeruginosa* *Klebsiella pneumoniae* *Enterococci*	Cross Transmission Use of multiple antibiotic therapy	*Error in hand washing and misuse of personal protective equipments*
2. Pre-existing Co-Morbids *Female patients*	Bacterial inoculums	Length of hospital prior to admission into ICU	Admission to ICU
3. Underlying disease *Diabetes mellitus*	Process of host colonization	Indwelling devices or catheters *Closed system/ open system* *Duration of catheterization* *Abnormal serum creatinine* *Long term duration of antibiotic use (yeast isolated)*	Insufficient Nurse to patient ratio *Poor hand washing* *Error in catheter care and hub care* *Anchoring catheter to thigh* *Periurethral area care* *Clamping catheter before moving patient* *Hanging urine bag below bladder level*
4. Severity of Illness	Antimicrobial resistance	Adequacy of therapy for primary infection	Non-adherence to asepsis practice
5. Nutritional status *Obesity*			
6. Endogenous			*Microbial colonization of drainage tube and bag*

(Table prepared from data of Lowbury et al., 1981; Castle & Ajemian, 1987; Tortora et al., 1994; Wenzel, 1997, pp.822-832, Trilla, 1994; Fernandez-Crehuet et al, 1997 Agarwal et al,2006)