Drugs 1999 Jul; 58 (1): 51-67
0012-6667/99/0007-0051/$17.00/0

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Current Guidelines for the Treatment and Prevention of Nosocomial Infections

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Contents

Abstract

Nosocomial infections (NIs) are among the most difficult problems confronting clinicians who deal with severely ill patients. The incidence of these hospital-acquired infections varies with the size of hospitals, with specialities of wards, and with many other factors such as length of hospital stay, local trends in antibiotic usage, nursing and hygiene conditions, hospital design and geographical distribution of patients at risk. An average incidence of NI can be estimated at 5 to 10%, with higher rates in large university hospitals, reaching up to 28% in the intensive care unit (ICU). Changing epidemiology of NI and emerging resistance

problems have resulted in evolving strategies of antibiotic usage in patients at risk. Several recent antibiotic resistance problems have been identified, for instance in Gram-positive organisms, and have been surveyed, in addition to those previously well known in Gram-negative bacilli. The choice of empiric antibiotic therapy for the treatment of any NI before microbiology is available has become a difficult challenge, requiring: (i) surveillance data on a regular basis of predominant organisms in units at risk; (ii) surveillance of the current resistance patterns of these organisms; (iii) identification of outbreaks involving the prevalent organisms, using modern molecular techniques for typing the strain and assess cross-contamination. In documented infection, monotherapy *vs* combination therapy has been often discussed in the treatment of serious Gram-negative hospital infections, but these concepts vary with the site of infection, the nature of organism involved and its pattern of resistance, the kind of antibiotic which may more or less quickly select resistant mutants. Antibiotic therapy concepts vary significantly between countries, and combinations either empirical or based on laboratory data are often preferred in European countries than in the US. Frequent collaborative studies and an increasing communication between experts of different countries, make guidelines and consensus conferences, established in a particular country, useful elsewhere and may contribute to improvement in the management of NI. Guidelines for the prevention and the control of NI are well established in many developed countries and they may have resulted in the improvement of the prevention and the treatment of NI. However, there is still potential progress that should be made, including individual preventive practices, improvement in nursing practices, control of antibiotic use, trend to shorten the hospital stay and early discharge from hospital, which results in significant cost savings.

Defined as an infection neither present nor incubating on admission, nosocomial infection (NI) is associated with increased morbidity and mortality in the intensive care unit (ICU). By prolonging hospital stay of patients, NI adds significantly to the economic burden of managing the underlying disease which has led to hospitalisation of the patient.

More than 90% of reported NIs are bacterial, whereas viral, fungal or protozoal agents are less commonly involved in hospital-acquired infections. Nosocomial pathogens have evolved significantly in the past decades and severe infections caused by *Mycobacterium tuberculosis* and *M. avium* have become more common in association with the advent of infection with HIV. Similarly, opportunistic fungal pathogens have become increasingly involved in NI; severe fungal infections have been attributed to aggressive surgical procedures, organ transplantation, use of chemotherapeutic drugs in cancer and to the development of HIV infection.

This review deals with bacterial nosocomial pathogens only, since they are by far the major causes of NI. Neither tuberculosis and mycobacterial infections are included in this review because of the importance of the problem which requires a specific chapter, those diseases concerning not only hospitals, but also expanded worldwide, nor hospital-acquired viral infections which require specific management. We will concentrate our analysis on bacterial NI and preventive and therapeutic measures of NI occurring in the ICU.

1. Epidemiological Features of Nosocomial Infection (NI)

Several observations using longitudinal surveillance of NI in the same areas have underlined the evolving profile of NI. Large surveys carried out in

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the US and in European countries have pointed out that significant changes in both the incidence of various body sites of NI and the distribution of pathogens have occurred over the last 2 decades.[1-5] Moreover, emerging opportunistic new pathogens with new resistance problems have been noted as additional factors which have resulted in the changing patterns of NI.

1.1 Changes in the Distribution of Infection Sites

The predominant sites of NI may vary in different types of ICU. Early observation [Study of Efficacy of Nosocomial Infection Control (SENIC) Project 1975 to 1976] had shown that among NIs urinary tract infections (UTIs) predominated with a 42% incidence rate, followed by surgical wound infections (24%) and only 11% for respiratory tract infections.[6]

1.1.1 Pneumonia – Bacteraemia

Among sites of NI the most serious infections are pneumonia and bacteraemia. As seen in table I, significant changes have occurred in the incidence of pneumonia, from ≈15 to 17% in the early 1990s to reach up to >30% in 1995 and even to 46.9% in more recent European surveys.[2,4,5,7] Primary bacteraemia remained at lower rates of incidence (>12 to 13%), being stable at a rate of about 15%. It is to be noted that figures do not vary significantly between countries, even from both sides of Atlantic Ocean with, however, a higher rate of nosocomial pneumonia in Europe.

1.1.2 Urinary Tract Infections

UTIs that have for a long time been the major manifestation of NI, (30 to 40% until early 1990s) have decreased, probably in relation to improvement in surveillance and prevention measures as well as better care of urinary catheters.[8] However, UTIs still rank second after pneumonia and constitute an anatomic source of severe secondary bacteraemia.[9]

1.1.3 Bacteraemia, Sepsis and Septic Shock

With increased use of invasive procedures, cancer chemotherapy, immunotherapy and advances in organ transplants, a progressive increase in the incidence of sepsis and septic shock has been noted, often related to secondary bacteraemia,[2] with Gram-negative bacilli as predominant pathogens, but including also Gram-positive organisms. Primary bloodstream infections may involve major nosocomial organisms with, among Gram-positive bacteria, *Staphylococcus aureus* and coagulase-negative staphylococci (C-NS).[10]

A recent study in 24 French hospitals has shown a rate of severe sepsis in 6/1000 admissions, and 41 times more frequently in the ICU (119/1000) than in wards (2.9/1000); bacteraemia was associated with sepsis in two-thirds of cases[9] confirming the frequent occurrence of severe sepsis during septicaemia. The mortality rate depends on the underlying disease and, in rapidly fatal underlying

Table I. Changes in distribution of infection sites in nosocomial infections

Predominant infection sites (%)	American surveys[1,6]				European studies (EPIIC)[2,4]		France (EPIIC)[4]
	1975-76	1984	1990-92	NNIS[5] 1996	1993	1996	1993
Urinary tract	42	38	30-33	27.2	19	17.6	19.3
Respiratory tract	11	18	15-25	17.3	39	46.9	39.4
Septicaemia	5	7.5	13	15.8	15	12-13[a]	15.2
sepsis – septic shock						2.9-11.9	
Wound/surgical infections	24	17	≈15	18.7	3	6.9	7.5
Skin and soft tissue infections	9	5.7	≈15	2.1	15	4.8	3.9
Miscellaneous (meninges, bones, genital tract, gastrointestinal tract)	18	≈14	≈12		≈10	10.8	8.5

a Primary bacteraemia.

EPIIC = European Prevalence of Infection in Intensive Care; **NNIS** = National Nosocomial Infections Surveillance.

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pathologies, it may reach up to 55% of cases. The highest mortality rate was seen in patients with a respiratory source of septicaemia, and a Gram-negative bacteraemic pneumonia; high rates of secondary bacteraemia are seen also after surgical wound infections (6.6%),[11] and in cardiac surgery service (9.0%).

1.1.4 The Rates of Other Infection Sites

The rates of other infection sites of NI vary as a function of types of units: in surgical wound infections and in skin and soft tissue infections (SSTI), seen in surgical and burn units, environmental factors play a significant role in the incidence; reservoirs and sources of microorganisms, presence of contaminated wounds, personnel and contact transmission are responsible for persistent rates of 8 to 15% of SSTI and surgical wound infections (table I).[6,11-13] Less frequent sites of NI, secondary meningitis, gastroenteritis (occasionally pseudomembranous enterocolitis caused by *Clostridium difficile*) can be seen in the ICU but not often in a context of outbreaks of NI and only in selected cases of patients with specific risk factors. Nosocomial transmission of *Mycobacterium tuberculosis* is increasingly seen even in developed hospitals and occurs in American hospitals as well as in European institutions.[4,6,8]

1.2 Changes in Microbial Epidemiology

1.2.1 The Distribution of Pathogens

The distribution of pathogens responsible for NI has evolved over years. In the early antibiotic era, hospital-acquired infections were dominated by staphylococcal infections, well controlled initially by penicillin.[14] Then, as staphylococci became β-lactamase producers, β-lactamase stable compounds controlled Gram-positive infections. Then methicillin-resistant *S. aureus* (MRSA) and Gram-negative bacilli emerged as agents responsible for NI. In the late 1960s resistant Enterobacteriaceae (*Klebsiella* spp., *Serratia* spp.) became increasingly involved in NI[14,15] and in the years 1975 to 1980, the emergence of multiresistant aerobic Gram-negative bacilli *Pseudomonas aeruginosa, Acinetobacter* spp.) was observed in most European and American surveys, presenting difficult therapeutic problems.[16-18]

More recent surveys have indicated the re-emergence of Gram-positive cocci including coagulase-positive and -negative staphylococci and streptococci,[19] whereas Enterobacteriaceae tended to decrease from 23 to 16% and from 7 to 5% for *Escherichia coli* and *Klebsiella pneumoniae*, respectively.[14,20] Convergent reports underlined the increasing incidence of Gram-positive pathogens,[21] C-NS, enterococci[22,23] and of multiresistant *S. aureus*[24,25] as significant nosocomial pathogens. Newly recognised Gram-positive species include *Corynebacterium jeikeium* and *Rhodococcus equi*.[26,27] In addition, all surveys report the increasing incidence or simultaneous persistence of *P. aeruginosa*, *Acinetobacter* spp., and emergence of newer nosocomial Gram-negative organisms such as *Burkholderia cepacia* and *Stenotrophomonas maltophilia*.[28-30] The role of *Candida* spp., mainly in the form of nosocomial candidaemia, with increasing prevalence of *nonalbicans* species was underlined in recent surveys with an excess mortality of 38 % being attributable to candidaemia.[1,2,7]

1.2.2 The Current Incidence of Leading Nosocomial Pathogens

The current incidence of leading nosocomial pathogens by site of infections is summarised in table II, reporting data from the US National Nosocomial Infections Surveillance[1,5] and from European countries [European Prevalence of Infections in Intensive Care (EPIIC) Study].[2,4,17] There are no significant differences between American and European data in the incidence of major nosocomial pathogens. Of note is the higher incidence of enterococci in bacteraemia in the US, a higher prevalence of *Acinetobacter* spp. in European countries, a higher incidence of *P. aeruginosa* in nosocomial pneumonia and in UTIs in France. However, in all surveys, most organisms were seen in approximately similar rates in the 4 main sites of NI.

1.2.3 The Distribution of Pathogens in Specific Site

The distribution of pathogens in specific sites as summarised in table III shows that Gram-negative

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Table II. Leading nosocomial pathogens by site and frequency (%) [adapted from[1,4,5]]

Site	No. of organisms	Data from NNIS[5] (138.925)[a]	European countries (EPIIC) (1.755)	France (EPIIC)[4] (493)
Lower respiratory tract infection	*Pseudomonas aeruginosa*	20.8	29.8	34.8
	Staphylococcus aureus	17.1	31.7	36.8
	Enterobacter spp.	11.1	C-NS: 10.6	5.0
	Acinetobacter spp.	6.4	*Acinetobacter* (9.9)	10.0
	Klebsiella pneumoniae	5.6	*E. coli* (6.8)	4
				Candida (7.0)
Urinary tract infection	*Candida* spp.	25	21.2	23.4
	Escherichia coli	17.5	21.2	28.1
	Enterococci	13.4	15.9	10.9
	P. aeruginosa	11.3	-	17.2
	Enterobacter spp.	6.1	15.0	-
			Klebsiella 6.8	9.4
Bacteraemia	C-NS	28.2	44.9	49.3
	S. aureus	16.1	21.9	21.3
	Enterococci	12.0	-	-
			6.5	4.0
	Candida[b]	10.2	9.3	-
	Enterobacter spp.	5.3	*K. pneumoniae* 4.5	4.0
	P. aeruginosa		9.7	6.7
Surgical wounds	Enterococci	15.8	18.2	12.2
	C-NS	13.8	35.6[c]	2.4[c]
	S. aureus	11.7	26.5	34.1
	Enterobacter spp.	10.3	(18.2)[d]	(19.5)[d]
	P. aeruginosa	9.5	-	14.6
	E. coli	-	12.9	7.3
			Candida (8.9)	2.4

a All infection sites.

b And other fungi.

c All Gram-positives.

d All Enterobacteriaceae.

C-NS = coagulase-negative staphylococci; **EPIIC** = European Prevalence of Infection in Intensive Care; **NNIS** = National Nosocomial Infections Surveillance.

organisms predominated in burn wound infections whereas Gram-positive pathogens were the leading cause of bacteraemia[25,31] (either primary bloodstream infection or catheter infections). In nosocomial pneumonia, there is an equal incidence of *P. aeruginosa* and *S. aureus*, both being the predominant organisms as in the EPIIC study, but other Gram-negative organisms are potentially difficult-to-treat nosocomial pathogens (*Acinetobacter* spp.,[16] *Enterobacter* spp.[32]) with, in addition 'renaissance' of the pathogenic role of *Streptococcus pneumoniae*, considered today as a potential nosocomial agent.[19]

2. Management of NI

Many antimicrobial agents are available today in hospitals, and antibiotic therapy should theoretically be chosen when the infecting organism and its susceptibilities have been established in a given infection. More frequently, and particularly in the ICU, antibiotic therapy is empirical because of emergency situations, severity of infections observed in immunodepressed, neutropenic and elderly patients, and patients with any other severe underlying disease. Optimal therapy in those difficult-to-treat situations should take into account the

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local microbiological backgrounds in each ICU, (prevalent organisms), and their current resistance patterns. The most appropriate empiric treatment is best achieved on the basis of resistance surveillance.

2.1 Susceptibility Resistance Backgrounds

Resistance to first-line antibiotics has been defined for each nosocomial organism and recognised in various countries: several β-lactamases, produced either chromosomally (cephalosporinase) or plasmid mediated in *P. aeruginosa*,[32,33] conferring resistance to antipseudomonal penicillins and cephalosporins; methicillin and fluoroquinolone resistance in *S. aureus*;[25] vancomycin resistance in *Enterococcus faecium*;[23] and in *K. pneumoniae* production of extended spectrum β-lactamases that can be found in other Gram-negative organisms.[33]

Emerging organisms such as *Acinetobacter baumannii*, *S. maltophilia* and *B. cepacia*[28-30]were generally multiresistant at first, as opportunistic bacteria were selected by exposure in patients and in hospital environment to factors promoting their pathogenicity, such as the large usage of broad spectrum antibiotics. The key resistances in the main nosocomial organisms are summarised in table IV. More information for Gram-negative[28,32-36,38-42] and Gram-positive organisms[19,22-27,31,43] can be found elsewhere.

2.2 Strategies for Management of NI: Empiric Therapy

2.2.1 General Considerations

The changing epidemiology of NI and emerging resistance mechanisms have resulted in evolving empirical strategies of antibiotic usage in patients at risk. The choice of empiric antibiotic therapy for the treatment of any NI before microbiology is available requires: (i) surveillance data on a regular basis of predominant organisms in units at risk; (ii) surveillance of the current resistance patterns of these organisms; and (iii) identification of outbreaks of NI involving one or more prevalent organisms.

The early identification of infection site, for instance, of potential bacteraemic pneumonia and of sepsis risk, based on combination of fever or hypothermia, tachycardia, tachypnoea and/or signs of organ dysfunction, should lead physicians to rapid decisions concerning resuscitation measures and antibiotic coverage of potential nosocomial pathogens.[2,9,44] The prevalence of pathogens in

Table III. Incidence of nosocomial organisms in other specific infection sites (adapted from [1,2,8,10,11,25,31])

	Long term central catheters (%)[1,8]	Short term central venous lines (%)[1,8,25]	Primary bloodstream infection (%)[8,25]	Burn and surgical wounds (%)[11]
Gram-positives	**60-80**	**40-60**	**56.3**	**41**
C-NS	40-60	30-50	27.7	2
Staphylococcus aureus	20-30	5-15	16.3	26
Enterococci	5-10	5-10	8.5	12
Streptococci			3.8	1
Gram-negatives	**15-25**	**30-40**	**27.7**	**55**
Serratia spp.	5-10	5-15		
Acinetobacter spp.	1-5	3-5		3
Enterobacter spp.	5-10	5-10	5.0	9
Klebsiella spp.	5-10	5-10	4.5	3
Pseudomonas aeruginosa		1-5	4.4	21
Escherichia coli	1-5	1-5	6.0	8
Fungi	**5-10**			
Candida spp.	5-10	3-5	7.8	5

C-NS = coagulase-negative staphylococci.

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Table IV. Current resistance problems in important nosocomial pathogens

Organisms	Key antibiotic resistance	%	Mechanisms
Gram-negative bacilli[28,32-36]			
Enterobacteriaceae			
Klebsiella spp.	• β-lactams ESBL (R to cefotaxime; ceftazidime; aztreonam)	1-58[a]	Plasmid mediated β-lactamases
	• Fluoroquinolones	8-32[a] (>80%)	Affinity to target DNA gyrase
Enterobacter cloacae	• Bush group 1 β-lactamase:		
	ceftazidime third generation cephalosporins	38	Chromosomally mediated cephalosporinase
	• Imipenem resistance	1-9	Permeability problems, imipenemase
Aerobic Gram-negative bacilli			
Pseudomonas aeruginosa	• β-lactams (same profile as *P. aeruginosa*)		
	third generation cephalosporins	2-28	Chromosomal cephalosporinase
	penicillins: carboxy penicillins	16-38	Plasmid mediated: PSE; OXA; CARB; TEM enzymes
	penicillins: ureido penicillins	5-22	
	imipenem	8-40	Imipenemase; altered outer membrane protein
	• Aminoglycosides	≈46	
	• Fluoroquinolones	5-13	
Acinetobacter baumannii	• β-lactams (same profile as *P. aeruginosa*)		Same mechanisms as *P. aeruginosa* (β-lactamases)
	• Aminoglycosides, higher rates of resistance	30-98	Aminoglycoside inactivating enzymes)
	• Quinolones	≈85	
	• Imipenem	0-5	β-lactamase ARI-1; permeability problems
Gram-positive organisms[2,19,25,31,37]			
Staphylococcus aureus	• Penicillin-resistant; methicillin-resistant (MRSA)	90 (≈60)	Penicillinase: altered target (PBP2A)
	• MRSA: all β-lactams	100	Efflux
	fluoroquinolones	30-100	Altered DNA gyrase
	glycopeptides	Rare	Reduced susceptibility (occasional)
Coagulase-negative Staphylococci	• Methicillin resistant:	>70	Altered receptors
	macrolides, clindamycin, tetracyclines, cotrimoxazole	R	
	• Quinolones	65	
	• Vancomycin	1-3	Same as *S. aureus*
	• Aminogycosides	(≈65)	
Enterococcus spp.	(Naturally resistant to cephalosporins)		
E. faecalis	Ampicillin-R	1-3	Plasmid mediated transferable
	Vancomycin-R	0.2-22	Mechanism: altered D-ala-D-ala, Pentapeptid target
E. faecium	Ampicillin-R	20-82	β-lactamase <1%: altered PBP >20%
	Vancomycin	1-42	Altered DNA ligase
	Teicoplanin	(72[b])	
	Gentamicin (high level)	≥50	Aminoglycoside inactivating enzymes

a Personal data.

b 72% susceptible to teicoplanin among vancomycin-resistant enterococci (Van B phenotype).

ESBL = extended spectrum β-lactamase; **MRSA** = methicillin-resistant *Staphylococcus aureus*; **PBP** = penicillin-binding protein.

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severe sepsis and septic shock in adults has been established, with *E. coli* (14.2%), *S. aureus* (18.2%), *P. aeruginosa* (13.5%), *Klebsiella*/*Proteus* (11%) and enterococci (5.9%) as predominant organisms.[9] Another example is nosocomial pneumonia which often requires empiric therapy broad enough to cover the large numbers of suspected nosocomial pathogens: local bacterial sensitivity patterns as well as local circumstances (epidemics) should always be considered in deciding on empiric therapy.[45,46] In that particular site of NI there is an important parameter that should contribute to therapeutic decision: the 'timing' of onset of nosocomial pneumonia which should not be treated in case of early onset by the same regimen as in late onset of the disease.[45,46]

2.2.2 Principles of Empiric Therapy

Despite the multiple facets of NI in terms of patient background, site of infection, diversity of organisms involved and their patterns of resistance and potential polymicrobial infection, conventional empiric therapy has to be broad enough to ensure coverage of most Gram-negative bacilli, such as highly resistant *P. aeruginosa*, *Serratia marcescens*, *Enterobacter cloacae* or *A. baumannii* as suggested particularly in nosocomial pneumonia, which is the second most frequent NI in the ICU.[45,46] Combination therapy with an antipseudomonal penicillin plus an aminoglycoside, or an antipseudomonal cephalosporin (cefsulodin, ceftazidime) plus an aminoglycoside have been for long the initial regimen recommended officially. However, in situations suggestive of Gram-positive organisms such as MRSA in institutions where this organism is endemic, the addition of a glycopeptide forms part of empiric therapy.

Other antistaphylococcal drugs such as rifampicin (rifampin), clindamycin, fusidic acid and streptogramins should cover most Gram-positive organisms; but combinations of fusidic acid or of rifampicin (prone to select resistant mutants) with other drugs for broad coverage are not easy to use empirically and require careful *in vitro* susceptibility testing.

During outbreaks of NI, with high probability of cross-contamination of a previously identified endemic multiresistant organism such as *P. aeruginosa*, carbapenems (imipenem-cilastatin, meropenem) in combination with either an aminoglycoside (amikacin) or a fluoroquinolone (ciprofloxacin) should be recommended.[47]

Any empirical therapy, whatever the strategy used and adapted to the particular condition of the patient, should always be reassessed 2 or 3 days after the initiation of therapy. This is an important stage in the follow-up of the treatment that should be readjusted on the basis of the microbiology, available on day 2 or 3, on the clinical response in the patient, on the potential choice of more suitable combination therapy or on the potential switch to less expensive/toxic antibiotics when the clinical status of patient suggests to do so.

2.2.3 Specific Empiric Situations

When the context suggests the potential role of anaerobes, generally associated with aerobic bacteria, for instance in surgical abdominal polymicrobial infection or in aspiration pneumonia,[48] the addition of clindamycin or cefoxitin or metronidazole is recommended. Imipenem is a useful alternative for mixed aerobic-anaerobic infections.

If legionellosis is suspected in the presence of atypical pneumonia, potentially in relation to environmental factors (contamination of hot water distribution systems or cooling towers), intravenous erythromycin and rifampin either alone or in combination are the antibiotics of choice.[46]

Identification of patients at early stages of sepsis and organ dysfunction is an emergency situation, prerequisite of multiple organ failure or dysfunction syndrome (MODS),[10,44,47] The predominant organisms which contribute to the severity of MODS originate from the gastrointestinal tract (*E. coli*, *Bacteroides fragilis*, enterococci) and secondarily acquired nosocomial organisms (*P. aeruginosa*). They are responsible for translocation, endotoxin release and aggravation of the sepsis syndrome. Those cases require restriction policy of broad spectrum antibiotics and instead, use of nar-

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row spectrum antibiotics focused on specific organisms.

In febrile neutropenia, with neutrophil count 500/mm^3 and fever 38.3°C, recent strategies for empiric treatment have been established in the context of 1997 guidelines.[49] Initial antibiotic therapy in neutropenic febrile patients should be 1 of 3 regimens: (i) vancomycin plus ceftazidime if vancomycin is needed (colonisation with MRSA or with penicillin-resistant pneumococci or other Gram-positive resistant organisms, C-NS, *C. jeikeium*); (ii) if vancomycin is not needed, monotherapy: ceftazidime or imipenem (or cefepime or meropenem); if a combination is needed (iii) in dual therapy, the standard combination being ceftazidime plus an antipseudomonal β-lactam.[50,51]

2.3 Documented NI: Therapeutic Strategies

2.3.1 Preliminary Considerations

There are several important features in establishing a suitable therapy of a documented NI. The identification of the aetiological agent(s) involved in a given NI and/or in an outbreak of NI should rely on an efficient clinical microbiology laboratory and good epidemiology practices within the hospital wards for the knowledge of local microbial ecology; moreover, the choice of a single agent or of a combination based on clinical considerations should also refer to the known patterns of susceptibility/resistance and *in vitro* combination tests.[34-36,39-41]

The patient's condition, the more or less severe underlying diseases, the presence of various devices (catheters, ventilatory equipment, protheses) are important factors which may interfere with the choice of a single agent or of a combination of antibiotics guided by the clinical condition of the patient. Clinical condition may be defined by means of scoring systems such as the MacCabe score, stratifying patients according to whether the underlying disease (Gram-negative bacteraemia) was fatal, ultimately fatal or nonfatal, or the APACHE II score system. The severity of the infection, the age of the patient and the underlying disease(s) as well as the site of the infection and the causative pathogen(s) have been used to propose 'severity-of-illness' scoring systems, proposed to estimate patient's risk of death,[10] which may help the physician to therapeutic decisions.

The site of NI and pharmacokinetic consideration are other factors leading to an appropriate choice of antibiotics: adequate delivery of the drug(s) in infected tissues depends on dosage and route of administration, and on local factors at the infection site, such as potential inactivation of aminoglycoside at low pH, high protein binding with limited amount of free drug, poor penetration in sites with barriers such as CSF (blood-brain barrier), and variable penetration of drugs into cells (macrophages) to reach and kill intracellular organisms (*Legionella pneumophila*).

2.3.2 Intrinsic Antibacterial Activities of Antimicrobial Agents: Monotherapy vs Combination Therapy

The *in vitro* interactions between bacteria and antibiotics as determined by standard techniques are by far more simple than in *in vivo* conditions and particularly in NI, characterised by a wide variety of host factors which may interfere with the antibacterial activity of antibiotics. Therefore, the spectrum of a given antibiotic, although promising on an *in vitro* basis, may result in treatment failure. Ceftazidime or ceftriaxone have good anti–Gram-negative activity but are poorly active against *S. aureus*. Imipenem-cilastatin offers broad spectrum antibacterial activity but a high risk of emergence of resistance during therapy in *P. aeruginosa*.

The use of a single agent or of combination therapy constitutes a matter of debate[52-55] as shown in several examples.

- Combination therapy superior to monotherapy: most retrospective studies have concluded that combination therapy is superior to monotherapy in treating aerobic Gram-negative bacteraemia. The European Organisation for Research and Treatment of Cancer performed a randomised trial that showed 81% success rate with ceftazidime plus long term amikacin *vs* 48% response rate with short-course amikacin; the latter had in addition more further infections

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than the long course, with *P. aeruginosa* bacteraemia.[54]

- Monotherapy comparable to combination antibiotic therapy: retrospective studies of patients with Gram-negative bacteraemia have shown a survival rate of 77% in patients with rapidly fatal diseases when individuals received 2 antibiotics *vs* 50% in patients who received 1 antibiotic, but statistical significance was not achieved in that particular study.[55]
- Comparison of a single drug *vs* combination (not including the single drug): a comparison of meropenem (monotherapy) with standard combination ceftazidime plus amikacin in granulocytopenic patients with cancer showed that the success rate in the meropenem group was similar to the combination group, with no further differences in occurrence of infections in both groups, and similar results were obtained by using ceftazidime *vs* ceftriaxone plus tobramycin or amikacin.[52,53]
- Monotherapy *vs* dual therapy in nosocomial pneumonia: the use of single agent antibiotic therapy in treating patients with nosocomial pneumonia was based on a third generation cephalosporin, imipenem-cilastatin, or a fluoroquinolone. The results from these studies have shown in general that monotherapy can be a useful alternative to combination therapy. However, in patients with severe infections caused by multiresistant bacteria like *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, a combination of an antipseudomonal β-lactam plus an aminoglycoside has proven more efficacious than monotherapy.[46]

2.3.3 Choice of Antibiotic(s) as a Function of Nosocomial Organism

The Role of the Microbiology Laboratory

When combination therapy is decided by the clinician, the synergy of selected combinations must be examined, since contradictory conclusions can be seen in the published data. For instance, combinations of penicillins plus a glycopeptide have been described as providing synergy against highly vancomycin-resistant enterococci, whereas an absence of synergy was concluded for ampicillin plus vancomycin against vancomycin-resistant *E. faecium* elsewhere.[56-58]

Rapid reporting of identification of pathogen(s) and of resistance patterns is expected from the microbiology laboratory, and all bacteriology data should be accessible to clinical team and infection control personnel.[6,39] Computer storage and transmission of laboratory data have become increasingly developed in many hospitals. A close collaboration between microbiologists, infectious disease consultants and 'intensivists' for surveillance of each case of NI may permit early detection of emergence of resistance during therapy or to identify a 'new' infecting organism as the initial pathogen has been eradicated.

Gram-Negative Organisms

Monotherapy (table V): Although less frequently used than combination therapy, monotherapy has been recommended, using a third generation cephalosporin (ceftazidime) or more recently cefpirome/cefepime,[59] or aztreonam in Gram-negative infections, the latter drug offering a narrow spectrum of anti–Gram-negative activities. The latter remark concerning aztreonam is of importance since with broad spectrum cephalosporins that have proven efficacious in most treatments worldwide, some drawbacks have been recognised, such as derepression of class I cephalosporinase.[60] The potential improvement of newer cephalosporins cefpirome/cefepime have been attributed to the return to antistaphylococcal activity as compared with cefotaxime/ceftazidime and a rapid intrabacterial penetration resulting from the zwitterionic character of these drugs.[59]

Other options for treating Gram-negative NIs are a β-lactam plus a β-lactamase inhibitor such as amoxicillin plus clavulanate or piperacillin plus tazobactam, commonly used in the treatment of severe pneumonia or UTI. Carbapenems are usually preferred to treat NI, since the high incidence of cephalosporinase producers, e.g. in *Enterobacter* spp. or in aerobic multiresistant bacilli, contribute to treatment failures using third generation cephalosporins.[53,61] Monotherapy in nosocomial

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Table V. Therapeutic strategies for documented nosocomial infections: monotherapy *vs* antibiotic combinations. Choice as a function of pathogens

	Monotherapy	Conventional combinations	Alternatives	Comments
Gram-negative organisms				
Escherichia coli	Ceftazidime or aztreonan or cefpirome/cefepime: amoxicillin-clavulanic acid: fluoroquinolone (in UTI)	Cefotaxime + amikacin: piperacillin + tazobactam: cefoxitin or aztreonam + aminoglycoside	Imipenem alone: imipenem + aminoglycoside: imipenem + fluoroquinolone	Increasing rates of ESBL production in *E. coli* (≈5.4%): fluoroquinolone resistance 28%[34]
Klebsiella spp.: ESBL–	Ceftazidime or cefoperazone or cefepime/cefpirome: amoxicillin-clavulanic acid	Piperacillin + tazobactam: ticarcillin + clavulanic acid: cefotaxime + aminoglycoside	Imipenem alone: imipenem + aminoglycoside: imipenem + fluoroquinolone	1.5 to 3.6% ceftazidime R: 1 to 58% ESBL (outbreaks), fluoroquinolone R (≈8-80%): importance of susceptibility testing
ESBL+	Imipenem or cefepime: fluoroquinolone (in UTI)	Imipenem + aminoglycoside: piperacillin + tazobactam + amikacin	Imipenem + ciprofloxacin	Detection of ESBL production
Enterobacter spp.	Imipenem or meropenem: cefpirome/cefepime: piperacillin + tazobactam	Third generation cephalosporin + aminoglycoside: aztreonam + amikacin	Imipenem + fluoroquinolone: aminoglycoside + ciprofloxacin	Importance of detection of Bush group 1 cephalosporinase[60] (14-56%): detection of imipenem-R: cefepime inhibits 97% of ceftazidime-R strains[50]
Pseudomonas aeruginosa	Penicillins (ticarcillin, piperacillin, azlocillin). Cephalosporins (ceftazidime, cefpirome/cefepime), imipenem, meropenem	Ticarcillin, aztreonam or ceftazidime + sulbactam + tobramycin or amikacin: imipenem + amikacin: ceftazidime + fluoroquinolone	Antipseudomonal penicillin + fluoroquinolone: aztreonam + amikacin: aminoglycoside + ciprofloxacin: fosfomycin + ciprofloxacin	Ceftazidime-R: stable (≈10%), higher for cefotaxime (35-70%): outbreaks of imipenem-R strains: increasing R to quinolones (>18%)
Gram-positive organisms				
Staphylococcus aureus: MSSA (methicillin–susceptible)	Penicillins, cloxacillin: cefazoline, cefalothin: second generation cephalosporin: cefotaxime: aminoglycosides	Penicillin + aminoglycoside (oxacillin + gentamicin): tetracycline + aminoglycoside: amoxicillin-clavulanic acid: ampicillin + sulbactam	Fluoroquinolone + fusidic acid: fosfomycin + β-lactam: synergistins (streptogamins): oxacillin: fusidic acid + cloxacillin	High risk of emergence of R mutants by using: rifampicin (rifampin), fosfomycin, fusidic acid, fluoroquinolones in monotherapy
MRSA (methicillin–resistant)	Vancomycin: imipenem-cilastatin: meropenem: fusidic acid	Rifampicin + vancomycin: fusidic acid + glycopeptide: fosofomycin + aminoglycoside: vancomycin + fluoroquinolone	Imipenem + vancomycin: fusidic acid + fosfomycin: fusidic acid + glycopeptide: fusidic acid + rifampicin: synergistins	Choice of combination as a function of infection site: careful susceptibility testing of combinations for each strain[24,65-67]
Coagulase-negative staphylococci	Same indications as for MRSA, with higher resistance rates to: quinolones, aminioglycosides, clindamycin, cotrimoxazole		Imipenem + fosfomycin: aminoglycoside or synergistins	Difficult to treat infections
Enterococcus spp.	Ampicillin: imipenem: piperacillin: glycopeptide (in nosocomial UTI only): synergistin	Ampicillin + gentamicin: vancomycin + aminoglycoside	Teicoplanin + penicillin: imipenem + glycopeptides: piperacillin + teicoplanin	*E. faecium*: increasing resistance to β-lactams, imipenem, vancomycin [57,58]

ESBL = extended spectrum β-lactamase; **R** = resistant; **UTI** = urinary tract infection.

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pneumonia can be based also on intravenous ciprofloxacin, which has been compared with imipenem in a randomised double-blind study, with no significant difference between regimens.[61]

Combination therapy (table V): More frequently recommended conventional antibiotic therapy in NI is based on synergistic combinations.[62] In the EPIIC study, in 62% of cases (out of 10 038 patients) the most frequently administered antibiotics were cephalosporins (44%), broad spectrum penicillins (24.3%), aminoglycosides (23.9%), fluoroquinolones (11.9%) and glycopeptides (11.6%), and half of the patients received more than 1 antibiotic.[2,4]

Besides conventional combinations of a β-lactam plus aminoglycoside which offer broad spectrum of antibacterial activity, the association of ciprofloxacin with ceftazidime in *P. aeruginosa* NI, although additive or indifferent *in vitro*, has shown efficacy and prevention of emergence of resistance during therapy. It has been confirmed that quinolones combined with a β-lactam (ureidopenicillin, ceftazidime or imipenem) reduce the risk of emergence of resistance in *S. pneumoniae*, *S. marcescens*, *E. cloacoe* and *P. aeruginosa.* Other unusual synergistic combinations such as ciprofloxacin plus fosfomycin against *P. aeruginosa* NI and ciprofloxacin plus imipenem against *Acinetobacter* infection have been used successfully.[37,48,63]

Gram-Positive Organisms

Multidrug-resistant Gram-positive organisms pose specific problems such as methicillin-resistant staphylococci that are also resistant to rifampicin, aminoglycosides and fluoroquinolones:[64] the current drugs of choice for treatment of MRSA infections are vancomycin and teicoplanin (table V).[65] Decreased susceptibility of MRSA to glycopeptides has been already cited and in C-NS as well.[66] Promising activities of a new streptogramin (quinupristin-dalfopristin) have been established in multidrug-resistant staphylococci and *E. faecium*: the latter species has been increasingly involved in NI unresponsive to vancomycin, imipenem, gentamicin and ciprofloxacin. Early clinical results, reported in 234 patients with enterococcal infections (*E. faecium* resistant to vancomycin) were favourable in 63% of all cases including bacteraemia (60%), intra-abdominal infections (23%), catheter-related bacteraemia (10%) and endocarditis 4%.[67]

2.3.4 Antibiotic Therapy as a Function of NI Site: Selected Examples

Nosocomial Pneumonia

The lung parenchyma and bronchial tissues are generally reached by penicillins, third generation cephalosporins and fluoroquinolones at concentrations high enough to inhibit most organisms susceptible or moderately susceptible to these drugs.[68,69] However, the multiple mechanisms of resistance exhibited by the 2 major pathogenic organisms, *P. aeruginosa* and *S. aureus* (table IV) impose the use of combinations of synergistic antibiotics (β-lactams plus aminoglycosides) as indicated in table V. A specific problem is that related to the early observation of *S. aureus* strains with reduced vancomycin susceptibility which should lead to the increasing use of newer compounds such as quinupristin-dalfopristin.

Similar problems have been seen with *Enterococcus* spp. In addition, although less frequently isolated from nosocomial pneumonia, *S. pneumoniae* has become a worldwide problem because of its increasing resistance to penicillin and to most β-lactams.[19] The latter problem can be solved by using high doses of benzylpenicillin (penicillin G) or with third generation cephalosporins (ceftriaxone or more recently developed drugs like cefpirome and cefepime). These antibiotics reach high lung parenchymal concentrations (up to 57.4 ± 13 mg/kg for ceftriaxone and high levels are also found in epithelial-lining fluid and in bronchial mucosa).[69]

Specific conditions such as severe *Pseudomonas* nosocomial pneumonia or superinfection in cystic fibrosis patients may require achievement of higher tissue concentrations. Topical antibiotic therapy may result in significant increase of local antibiotic concentrations so that free drug exceeds the minimum inhibitory concentrations of pathogens.[68,70] A good clinical tolerance was reported

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for gentamicin, tobramycin, and amikacin, even though some reduction of the maximum expired volume per second has occasionally been observed; carbenicillin and ceftazidime were also administered topically and were well tolerated.

Bacteraemia: Nosocomial Bloodstream Infection

There are several sources of bacteraemic extension, mainly nosocomial pneumonia and UTI. Other foci of infection such as SSTI (particularly in burn patients), and surgical wounds are less often the source of bacteraemia.[10] Gram-positive organisms, MRSA and C-NS exceed Gram-negative bacilli (table III) partly in relation to the presence of intravacular devices, central lines or peripheral intravenous catheters. Specific problems in antibiotic effects on staphylococci adherent to catheters have been described:[71] C-NS produce an extracellular slime matrix in which bacteria are embedded and which interferes with the penetration of antibiotics: bacteria cannot be eliminated by traditional antimicrobial therapy. Only continuous infusions of combinations of imipenem plus fosfomycin, or vancomycin or an aminoglycoside seem to offer potential efficacy. Removal of intravenous catheters constitutes the only therapeutic measure in most cases.

Whatever the infection site as a source of bloodstream infection, the mortality rates of bacteraemia range between 25 and 50%.[9,10,72] Monitoring must take into account the organism(s) isolated from blood, the identified source of the bloodstream infection and the potential participation of sepsis signs: thus, antibiotic therapy even suitably adapted to the nosocomial pathogens involved, is not sufficient. The patient's condition requires additional measures such as antiendotoxin antibodies or newer antiendotoxin and anticytokine therapies.[10]

Skin and Soft Tissue Infections

Among hospital-acquired severe SSTIs that are generally polymicrobial (cellulitis), one selected situation particularly difficult to treat and control is that of burn wounds. Besides topical wound care using various measures and disinfectants (0.5% silver nitrate solution, 10% mafenide-acetate cream or silver sulfadiazine), preventive antibiotics constitute the best approach to prevent wound infection.[11] Conventional systemic antibiotic therapy, although controversial, is recommended for prevention of infection immediately after burn injury when host defences are reduced, and during excision of colonised burn eschar, which is a frequent source of bacteraemia.

Treatment of invasive infection requires a systemic antibiotic therapy adjusted against the causative organisms, predominantly *P. aeruginosa, S. aureus,* or less frequently *A. baumannii*. Treatment requires an early initiated powerful combination of antibiotics. However, frequent emergence of resistance occurs in relation to high bacterial local counts and because of the limited access of antibiotics to burn sites.[73,74]

Paediatric NI

NIs differ from those in adults in regard to several characteristics: (i) their incidence is inversely correlated with age of children; (ii) the predominant sites of infection are digestive tract, respiratory tract and bloodstream; (iii) the predominant nosocomial pathogens are Gram-positive organisms; (iv) there is a high risk of bacteraemia with secondary infection sites (meningitis, bones and joint infections) and high mortality rates.

Management of NI in children is particularly difficult because of problems in collecting specimens for microbiology diagnosis and as a result in defining suitable therapeutic strategies.[75]

3. Strategies for Prevention

Prevention plays a major role in the control of NI. Numerous guidelines have been established in the US and in European countries based on conference consensus. Hospital infection committees are increasingly organised in modern hospitals to provide advice regarding the control and prevention of NI.[76,77]

Many prevention measures have been recommended, as summarised in table VI. Isolation policies, administrative and regulatory measures and hospital epidemiology surveillance are increasingly applied to reduce morbidity, length of hospi-

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Table VI. Strategies for prevention of nosocomial infection[8,10-12,76,78,79]

	General measures[78]	Nosocomial pneumonia[79]	Bloodstream infection[10]	Surgical wound infections[11,12]
Personnel	Educational programmes: hand-washing, gloves, gowns, etc.: control of infections at risk for healthcare workers: immunisation	Maintenance, disinfection of respiratory equipment (endotracheal tubes, suctioning devices, ventilators, etc.): careful use of invasive exploratory endoscopies	Careful manipulation of catheters: aseptic technique for insertion: experienced inserter: search for source of bacteraemia (infection foci)	Preparation of operative team (surgical gloves, gowns, masks, etc.)
Patient	Patient isolation: single room for high risk patients: antibiotic prophylaxis: controversial, specific conditions (neutropenic, burn patients): SDD: controversial:[82,83] topical treatments for colonised sites	Oropharyngeal decontamination: treatment of nosocomial sinusitis: local antibiotics (aerosols): gastric alcalinisation: semi-recumbent position: care of enteral nutrition	Duration of catheterisation, changed at appropriate intervals: adjusting for severity of underlying disease: blood cultures with best techniques (automated) for rapid identification of pathogens: SDD[a] limits translocation and endotoxin release	Wound classification (clean, clean-contaminated, dirty): minimise preoperation stay: suitable skin preparation, hair removal: antibiotic prophylaxis[13]
Treatment[80]	Optimal use of antibiotics. Control of antibiotic use (antimicrobial use audits)			
Environmental measures	Hospital nosocomial infection surveillance: close cooperation with microbiology: computerised systems in surveillance and fast transmission of data: proper elimination of medical waste	Surveillance of air conditioning humidifiers, hot water nebulisers (*Legionella*): isolation precautions: isolation guidelines	Hospital and intensive care unit surveillance (epidemiology): disposable catheters (instead of reusable): control of sterile infusates: close cooperation with microbiology	Limiting sources of exogenous contamination: excellent surgical technique, limiting 'dead space' exposing wound: proper wound dressing
Administration[76] (regulatory organisations, guidelines consensus conferences)	Infection Control Committee: restriction policies (hospital formulary): guidelines for prevention: consensus conferences: application of guidelines			Sterilisation and suitable disinfection measures for reusable equipment: disposable instruments whenever possible: disposal regulations
Miscellaneous	Hospital design engineers for suitable structure of wards, rooms, specific isolation units and health care facilities. Close cooperation between intensivists, microbiologists, infectious diseases consultants			

SDD = selective digestive decontamination.

tal stays, mortality and hospital costs. Among the published guidelines, 3 main approaches can be summarised as follows: First, methods based on elimination of endogenous nosocomial pathogens should reduce oropharyngeal, intestinal and skin colonisation in ICU patients. Second, use of methods to prevent cross-contamination and to control various sources of nosocomial pathogens that could be transmitted from patient to patient or from personnel to patient: proper disinfection and care of catheters, respiratory equipments, humidifiers, endotracheal tubes and dialysis systems. Third, use of antibiotic prophylaxis in postoperative high risk patients, either systemic antibiotics (burn patients) or local antibiotics or disinfection could be recommended to prevent contamination in burn patients, surgical wounds and the oropharyngeal area in ventilated patients. Aerosolised polymyxin-B and/or endotracheal aminoglycosides can be given to prevent *Pseudomonas* or *Acinetobacter* pneumonia which have the highest fatality rates.[45,68,70]

Specific immunoprophylaxis has been recommended in high risk situations against *Pseudomonas* and *Klebsiella* infections.[81] In addition, selective digestive decontamination (SDD) has been advocated in ICU patients.[82] Investigated for its effectiveness in preventing NI, the use of SDD should prevent colonisation of the oropharynx and the gut by potentially pathogenic bacteria: the digestive tract can be an important reservoir for mul-

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tiresistant organisms, particularly Gram-negative bacilli, and thus, the source of a variety of NIs. Topical chemoprophylaxis includes nonabsorbable antibiotics, generally polymyxin-E, tobramycin (or norfloxacin), and amphotericin B (the latter to control fungal colonisation). Most investigations included coadministration of systemic cefotaxime.

The strategy of topical application of the antibiotic combination comprises local application to the oral mucosa of a sticky paste and enteral injection of the mixture in the nasogastric tube. Many reviews have been published and have provided favourable results, but a clear consensus of effectiveness of SDD has not been established yet, possibly because of the heterogeneous groups of patients, varying oral regimens and inconstant addition of systemic cefotaxime or ceftazidime. Decreased rates of NI in SDD groups have been published[82] but the potential influence of SDD on mortality rates and otherwise on the duration of hospital stays remained inconclusive. Emergence of resistance during SDD and increased incidence of high level aminoglycoside-resistant enterococci and of MRSA have been discussed.[83]

4. Conclusion

In conclusion, prevention and control of NIs have evolved significantly over time. Improvement in hospital epidemiology surveillance, in infection control practices and in definition and application of guidelines for prevention of NI should result in decreasing incidence of morbidity and mortality caused by NIs. However, NI still remains a major threat in high-risk patients.

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