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Drug Resistance in Intensive Care Units

Summary: Intensive care units (ICUs) are generally considered epicenters of antibiotic resistance and the principal sources of outbreaks of multi-resistant bacteria. The most important risk factors are obvious, such as excessive consumption of antibiotics exerting selective pressure on bacteria, the frequent use of invasive devices and relative density of a susceptible patient population with severe underlying diseases. Infections due to antibiotic-resistant bacteria have a major impact on morbidity and health-care costs. Increased mortality is not uniformly shown for all of these organisms: Methicillin-resistant *Staphylococcus aureus* (MRSA) seems to cause significantly higher mortality, in contrast to vancomycin-resistant enterococci (VRE). Therefore it is essential to diminish these potential risk factors, especially by providing locally adapted guidelines for the prudent use of antibiotic therapy. A quality control of antimicrobial therapy within a hospital, and especially within the ICU, might help to minimize the selection of multidrug-resistant bacteria. The restricted use of antimicrobial agents in prophylaxis and therapy has also been shown to have at least temporal effects on local resistance patterns. New approaches to the problem of drug resistance in ICUs are badly needed.

Introduction

Intensive care units (ICUs) constitute 5–10% of all acute care hospital beds. The overall prevalence of nosocomial infections varies between 5–17%, however 20–25% of these are acquired in the ICU. The largest study on nosocomial infections in Western European adult ICUs, the European Prevalence of Infection in Intensive Care (EPIC) Study, showed a point prevalence of 20.6% ICU-acquired infections among 10,038 ICU patients in 17 countries. The variation between countries ranged from 9.7% in Swiss ICUs to 31.6% in Italian ICUs. Almost every second patient (44.8%) had evidence of infection and 45.9% of these infections were acquired in the ICU [1]. These rates also vary according to the type of ICU. Coronary care units showed the lowest nosocomial rates of infection with usually about 2% per patient [2]. The difference between surgical and medical ICUs is less marked, but surgical intensive care unit (SICU) patients tend to have higher rates of infection and more nosocomial urinary tract, wound, intraabdominal or CNS infections than medical intensive care unit (MICU) patients who develop pneumonia more often and suffer more frequently from community-acquired infections [3].

Major changes in health care systems are occurring worldwide with a tendency towards a shorter stay in the hospital and a subsequent reduction in general ward beds, and a relative increase in ICU beds. Simultaneously, inpatients are getting older and more severely ill, as advances in cardiovascular, pulmonary, oncological, transplantation and intensive care medicine keep them alive longer. Alterations of their immune status due to underlying disease or immunosuppression render them susceptible to infectious agents, with which they would never have become infected previously. These patients usually show the highest rates of invasive devices for diagnostic and therapeutic purposes which lead to a disruption of natural barriers. Mechanical ventilation, intravascular and urinary catheterization, stress ulcer prophylaxis and length of stay in the ICU are known risk factors for nosocomial infections; reversely, ICU acquired pneumonia, clinical sepsis and bloodstream infection were shown to be significant risk factors for increased mortality [1]. The rising importance of the ICU as a hot spot for the emergence and spread of infectious diseases in general and highly resistant agents in particular is highlighted by the increasing number of ICU beds – at least in relation to the total number of hospital beds. In addition, ICUs are the main source of outbreaks of infectious diseases in hospitals.

As patients become more susceptible to an increasing variety of microorganisms with critical resistance patterns, they are increasingly treated with the most potent antimicrobial agents covering both gram-positive and gram-negative bacteria, thereby exerting still greater selection pressure for resistant bacteria. This applies to the community but to a much greater extent to ICUs. As it is crucial for the survival of a critically-ill patient, the empiric antibiotic therapy in a suspected infection has to cover the most likely as well as the most dangerous microorganisms. Otherwise the incidence of crude mortality rises significantly; for example, for sepsis patient figures vary between an increase of 10–50% [4, 5].

Mechanisms of Resistance

The spread of antimicrobial-resistant microorganisms in ICUs is facilitated by the relative density of severely ill

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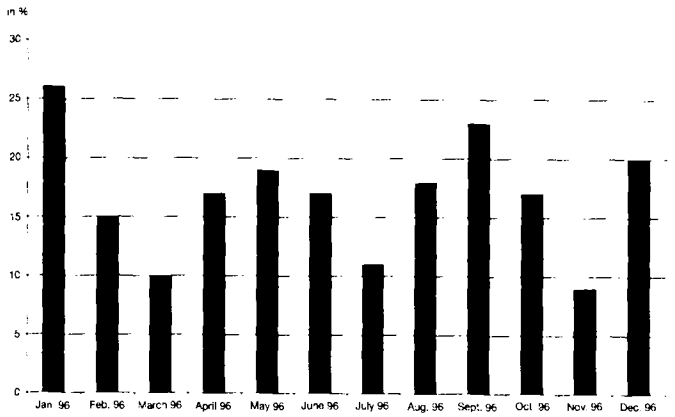

Figure 1: Catheters contaminated in 1996.

patients and thus an increased risk of transmission of these organisms via the hands of the health-care personnel (particularly *Staphylococcus aureus* and *Klebsiella pneumoniae*), or via inanimate objects like gloves, stethoscopes, electronic rectal thermometers or arterial pressure transducers [6] exists. Similarly, disinfectants have been implicated as reservoirs especially for multi-resistant gram-negative nonfermenters [7]. Particularly the introduction of already resistant microorganisms must be considered, if patients are transferred from other hospitals or long-term care facilities.

The much higher consumption of antibiotics in ICUs than in most other hospital departments reflects these facts. This is bound to lead to the selection of microorganisms inherently resistant to most of the commonly used antibiotics. Important examples of this mechanism are gram-negative bacteria such as *Pseudomonas aeruginosa* or *Acinetobacter* species [8].

Body sites with large amounts of bacteria, such as abscess formation, where they are shielded from antibiotics, for example, are reservoirs of bacteria prone to develop resistance merely by stochastic chromosomal mutations or transfer of resistance genes [9].

Transfer of mutated plasmids often carrying multiple resistance-mediating genes is a common mechanism of resistance in *K. pneumoniae*, frequently associated with an increased use of β-lactam antibiotics – especially third generation cephalosporins – but it also seems to disappear after the control of cephalosporin use and implementation of barrier precautions [10]. These extended spectrum β-lactamases (ESBL) can be transferred to other *Enterobacteriaceae* and mainly confer resistance to β-lactam antibiotics and monobactams, with the exception of carbapenems and cephamycins, and most aminoglycosides [6]. Promising results to control the emergence and spread of resistance due to ESBL producing *K. pneumoniae* by β-lactamase inhibitors were recently published [11]. Enterococci exchange genes with other gram-positive bacteria via plasmids and even more unrelated bacteria can transfer resistance genes via conjugation, transduction or transformation [9].

Fourth generation cephalosporins, suchs as cefpirome, as well as the carbapenems, appear to invade bacteria more quickly and by achieving bactericidal activity within a shorter time are probably less affected by plasmid or chromosomally mediated β-lactamases. Quinolones also face development of resistance because of their rising use. This is especially true for staphylococci and *P. aeruginosa* [12].

The ICU thus appears to be an ideal place for acquisition of antibiotic resistance, but the spread of those microorganisms not only within the ICU but also to other wards of the same or other hospitals is potentially dangerous, if appropriate barrier precautions are not carried out. Infections with resistant microorganisms have serious consequences such as significantly prolonged hospital stays, increased morbidity and health-care costs. However, there is debate about true mortality associated with resistant bacteria, because affected patients frequently suffer from severe or even untreatable underlying conditions. The EPIC Study and a group from Brazil showed mortality rates from methicillin-resistant *S. aureus* (MRSA) three and four times higher than from methicillin-susceptible *S. aureus* (MSSA) [13, 14], whereas others could not confirm these data [15]. In contrast, results for mortality due to vancomycin-resistant enterococci (VRE) bacteremia compared with those sensitive to vancomycin (VSE) do not show significant rises in mortality, but significantly longer hospital stays [16]. In comparison with historic controls without VRE bacteremia, however, a risk ratio for mortality of 2.3 for VRE bacteremia was reported [17].

Ways Out of the Dilemma

There are conflicting data about the use of combination therapy, e.g. an aminoglycoside with a β-lactam antibiotic, to reduce or prevent the development of resistance [12, 18]. Imipenem has a low induction potential for inducible β-lactamases, but failures to eradicate gram-negative nonfermenters have been reported, if used as single therapy [19]. *Moellering* reviewed the literature concerning the development of resistance in nontuberculous infections under antibiotic therapy. The principal organism posing a true threat of developing resistance under therapy was *P. aeruginosa* with 16.7–24.5% of cases, but there was no proof supporting the suggestion that combination therapy could indeed prevent this [20]. There is more of a consensus about the need for combination therapy for mycobacterial infections and endocarditis (especially enterococcal). A combination of imipenem and gentamycin for empiric therapy for suspected sepsis did not result in an increased rate of resistant bacteria [4].

Whether rotations of antibiotic therapy are of advantage, has to be investigated further. A scheduled change from ceftazidime to ciprofloxacin in low-risk cardiosurgical patients for empiric therapy of gram-negative infections, however, resulted in a significant reduction of the inci-

dence of ventilator-associated pneumonia, primarily due to a decrease in pneumonia caused by antibiotic-resistant gram-negative bacteria, and in a non-significant reduction in the rates of bacteremia due to antibiotic-resistant gram-negative microorganisms [21].
Selective decontamination of the digestive tract (SDD) with antibiotics for all ICU patients remains controversial. Advocators claim reductions in the rate of acquired pneumonia. Opponents point to the unsolved problem of the development of resistance, the trend towards the isolation of more antibiotic-resistant gram-positive bacteria and the lack of evidence of reduced mortality or length of stay. A recent metaanalysis detected a significant reduction in mortality by SDD for surgical patients only [22].
A large proportion of infections in the ICU is related to invasive devices. Of all the patients enrolled in the EPIC Study, 78.3% had intravascular catheters, 75.2% a urinary catheter, and 63% were mechanically ventilated at the time of study [1]. These pose significant risks of ICU infections and death.

Bloodstream Infections

The main pathogens isolated in the EPIC Study in laboratory-confirmed bloodstream infections were coagulase-negative staphylococci (44.9%; methicillin resistant in 70.1%), *S. aureus* (21.9%; methicillin resistant in 59.6%), enterococci (10.9%), *P. aeruginosa* (9.7%) and yeasts (9.3%) [1]. Primary bacteremia, catheter colonization and infection and bloodstream infection have to be differentiated and their incidence depends on various factors. Moreover, contamination must be excluded as it frequently leads to unnecessary and toxic antibiotic application resulting in additional selective pressure.
Essential impact is exerted by an aseptic technique while inserting and manipulating catheters. We observed higher rates of intravascular catheter infections every 4 months. There was an important association with the rotational training of new medical teams inserting the central venous catheters (Figure 1). In contrast, there was no improvement after the introduction of sterile surgical gowns for inserting intravascular lines.
The development of new materials such as catheters coated with aseptic materials (e.g. chlorhexidine with silver-sulfadiazine) [23] or antimicrobials (e.g. minocycline and rifampin) appears promising, at least for special indications of an increased risk of infection. The latter regimen showed significantly lower rates of catheter colonization (7.9% vs 22.8%), bloodstream infection (0.3% vs 3.4%), but only a nonsignificantly lower rate of nosocomial bacteremia (6.7% vs 10.2%). However, the long-term risk of antibiotic resistance is still unknown [24].
There does not appear to be a risk reduction if catheters are changed more frequently on a routine basis. Instead, change of catheter and site are advisable as soon as signs of infection occur either locally or systemically. If signs of infection disappear thereafter, there is no need for antibiotic therapy in our experience.

Respiratory Tract Infections

Nosocomial pneumonia is the most frequent ICU-acquired infection (46.9% of all nosocomial infections in ICU patients [25]) and also shows the highest mortality rate constantly being reported to exceed 40%. The main risk factor is mechanical ventilation. Increased mortality is observed with aerobic gram-negative bacteria especially *P. aeruginosa*, severe underlying disease, in particular neoplasms, inappropriate or previous antibiotic therapy, either very young or very old patients, shock, bilateral pulmonary infiltrates and hospitalization prior to ICU. In the EPIC Study, *S. aureus* (31.7%), *P. aeruginosa* (29.8%), *Acinetobacter* species (9.9%) and yeasts (14.0%) were the predominant species isolated from bronchopulmonary infection sites [25]. Again, it is crucial to distinguish between colonization and infection, but there is clearly a tendency towards previously rare and difficult-to-treat gram-negative microorganisms and the revival of gram-positive bacteria.

Vancomycin-Resistant Enterococci (VRE)

An increasing problem, particularly in ICUs, are VRE. Known risk factors are prolonged hospitalization, intrahospital transfer, prior and prolonged use of antibiotics – especially vancomycin, but also third generation cephalosporins – severe underlying disease, immunosuppression, intraabdominal surgery, enteral feeding and use of sucralfate [26, 27]. Within ICUs cross-infections and contaminated environmental sources have been implicated in VRE colonization or infection. Despite these clear-cut risk factors, some patients from the community are repeatedly reported to have none of them and most acquisitions apparently occur outside ICUs [28]. Much research is being done regarding the necessity and potential benefit of special precautions. Though recommended by the Hospital Infection Control Practices Advisory Committee (HICPAC) and the Centers for Disease Control (CDC), use of gloves and gowns by hospital employees did not result in fewer transmissions than gloves alone in a non-outbreak situation of VRE in a MICU. The authors emphasize that this might have been different in an outbreak setting and may be able to increase compliance [27].
Handwashing and disinfection are easy to perform and effectively prevent cross-transmission but usually show poor compliance – less than 40% among health-care personnel. Chlorhexidine has been shown to be superior to alcohol and soap, at least partly by achieving better compliance [29].
A main conclusion can be drawn despite all uncertainties: Antibiotic consumption is related to the development of resistance for an individual patient, the entire hospital

and for the global community [30]. Unfortunately there is little statistic power in these studies since they involve mainly individual institutions [31].

Local Characteristics Require Local Guidelines

Accurate knowledge of the most likely microorganisms and their antibiotic susceptibility patterns in a given situation is needed by the clinician. Since there are great differences between countries, hospitals and even wards, we recently established guidelines for a rational antibiotic therapy based on general recommendations but adapted to the local situation at our university hospital for internal medicine. With respect to commonly made mistakes, we outlined basic recommendations for antiinfective therapy. The endpoints of this database-associated study are the impact on resistance patterns, patients' outcomes, consumption and costs of antibiotics.

There is a great deal of evidence in the medical literature that local characteristics in changing epidemiology and antibiotic resistance patterns have been successfully encountered by local means of action. Especially the reduction of antibiotic consumption, in some cases even avoidance of any antibiotic prescription for a limited time, increased surveillance and prevention of cross-transmission have been effective in local outbreaks or situations of increasing resistance [32]. By computer-based decision support it was possible to reduce the number of applied antibiotics, the number of adverse drug effects, the number of days with excessive drug dosage and to decrease the number of drug-susceptibility mismatches, leading to a decrease in length of hospital stay and total costs. No significant difference in mortality was observed and no evaluation was made of the change in antibiotic susceptibility [33].

In our hospital there used to be a particularly high consumption of piperacillin/tazobactam and ceftazidime resulting in higher resistance rates of gram-negative bacteria especially against these antibiotics (e.g. *P. aeruginosa:* 21.9% and 24.9% in 1997) than would have been expected according to the EPIC Study. Following one of the major implications, we discouraged the empiric use of these two antibiotics especially for suspected gram-negative infections. In order to prevent the emergence of further resistance among inherently resistant microorganisms such as *Pseudomonas* spp., there was a recommendation for combination therapy with meropenem and tobramycin for proved infections until susceptibility data were available. In contrast, only 6.7% of all *S. aureus* isolates in the general wards and 7.3% in the ICUs have been resistant to methicillin since 1994 without any significant changes. An important message to the prescribing physicians was to use flucloxacillin primarily in suspected and proven *S. aureus* infections unless MRSA was detected.

It is necessary to distribute regularly updated versions of these guidelines to physicians. Compliance is likely to be increased by making the recommendations available in the intra-hospital computer network. By this kind of surveillance it should be possible to detect long-term trends earlier and to react more rapidly to short-term changes in specific antibiotic prescription and resistance patterns.

Future Challenges

Whether all these rather conventional measures will be sufficient to encounter the threat of increasing resistance and untreatable infections is more than questionable. A lot will depend on our ability to convince prescribing physicians of their personal responsibility for the emergence and spread of antibiotic resistance. Prudent and rational prescriptions of antibiotics adapted to local findings are essential, but their contribution to the problem unknown. Confining outbreaks of resistant organisms is crucial. However, this is probably more difficult to accomplish than the prevention of resistance.

Improvements in rapid diagnosis are desirable for a better and earlier selection of appropriate antibiotics with improved outcome for patients and possibly a reduction in antibiotic resistance. There will always be a call for new and more potent drugs. Bacteria will, however, inevitably evolve and rapidly adapt to a given situation. Despite this menace of a post-antibiotic era, various new approaches, including the development of vaccines, antisense nucleotides and investigation and attack of new targets and pathogenesis-related genes and geneproducts, appear promising.

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