Neurology Intensive Care Unit-Symptomatic Nosocomial Urinary Tract Infections: Management and Prognosis

Enas Hammad,1 Mohamed Saad,2 Hassan Salama.2
Departments of 1Medical Microbiology and Immunology, 2Neurology, Mansoura University

ABSTRACT

Background: Nosocomial urinary tract infection (NUTI) is the most common infections in intensive care unit (ICU) with a considerably high mortality and morbidity rates. It is a cause of concern and major pool of resistant pathogens. Objective: This is a prospective study conducted to detect the frequency of NUTI, common microorganisms, the risk factors and mortality in neurological ICU (NICU) at Mansoura University Hospital. Patients and methods: The current study enrolled patients who were admitted to NICU for ≥48 hrs from August 2009 to Sept 2010. Three hundred ninety-six patients (190 males and 206 females with median age 60 years) were enrolled in the present work. NUTI were diagnosed according to the CDC definition for patients who had urinary catheters. The following risk factors, age, sex, length of stay, duration of catheterization, immuno-compromized and risk of mortality, were studied. As well, isolation, identification and antimicrobial susceptibility were performed. An Enterobacter cloacae outbreak of UTI was detected. Typing and tracing of the source of infection was confirmed using ERIC-PCR. Results: NUTI frequency rate was 20.5%. The NUTI rate was high among old age, female, prolonged hospitalization, catheterization and immunocompromised patients. The mortality rate among NUTI patients was not significantly high. E. coli was the most common isolate (27.3%) which had maximum sensitivity to amikacin followed by meropenem. ERIC showed the same banding patterns among isolates from the three patients and hands of a nurse who was considered as the source of the outbreak. Conclusion: Prevention of NUTI clearly represents a real challenge that faces the health care field especially in ICUs. No doubt, effective interventions will be a critical step in the battle against antibiotic resistance and outbreak emergence in ICUs. Key Words: Nosocomial infection, risk factors, outbreak of enterobacter

INTRODUCTION

Nosocomial infections increased morbidity, mortality and resource expenditure. Few studies have addressed the issue of high prevalence and incidence of nosocomial infections in neurology ICUs.[4]

Urinary tract infection (UTI) is the most common nosocomial infections and the main source for nosocomial septicemia and related mortality world-wide.[2] Urinary catheterization is a routine procedure in neurology intensive care unit for monitoring urine output of critically ill and disabled patients.[3] Catheter-associated urinary tract infection (CAUTI) is a cause of concern and major pool of resistant pathogens.[4]

Outbreaks due to exogenous Enterobacter cloacae (E.cloacae) infection have been accounted in a range of clinical settings. E. cloacae could be responsible for urinary tract infection, bloodstream infection, and pneumonia in intensive care unit. E. cloacae prevalence as a nosocomial pathogen seriously increased since the widespread use of extended-spectrum Beta lactams, aminoglycosides and fluoroquinolones.[5,6]

Members of the genus Enterobacter, like other Enterobacteriaceae, are held responsible for opportunistic infections in debilitated and hospitalized patients. E. cloacae, a saprophytic micro-organism of normal digestive flora in humans is the most common isolated clinical species.[7]

Although UTIs are the most common hospital acquired infections, the epidemiology of these infections is not well established in Mansoura Neurology ICU. So, the current study was designed to detect the frequency, risk factors, mortality and common organisms causing Nosocomial Urinary Tract Infection (NUTI) and antibiotic sensitivity patterns in the neurological intensive care unit at Mansoura University Hospital. In addition, it was aimed to investigate the epidemiology of any detected outbreak together with tracing its possible source.
PATIENTS & METHODS

Study population.
This prospective study was conducted from August 2009 to Sept 2010 in the neurological intensive care unit (NICU) at Mansoura University Hospital. 396 patients (190 males and 206 females with median age 60 years) were enrolled in the present work.

The 7- bed neurological ICU is located in the neurology department which is situated in the specialized internal medicine building in MUH. Patients admitted in this unit for cerebral stroke (haemorrhagic or ischemic), respiratory failure secondary to neurological diseases (e.g. Gullain Barre syndrome, Myasthenia gravis), status epilepticus and metabolic-neurological disorders (e.g. electrolyte imbalance, organ failure).

During regular working hours two residents are in charge, with one specialist and one consultant neurologist as back-up. During night shifts, one resident is on duty and one specialist as a back-up. The normal nurse: patient ratio is 1:1 in working hours and 1:3 during night shift.

All patients were catheterized using indwelling urinary catheters (Foley’s catheter) under standard aseptic precautions. Major indications for catheterization were retention of urine, urine incontinence, severe motor disability and disturbed conscious level.

In the current study, the only symptomatic UTI criterion, in accordance with CDC criteria in patients who had urinary catheters, is fever that cannot be explained by other circumstances. (8)

The concerning risk factors in the existing study were Age, sex, immune-compromised status (immunosuppressive drugs, renal failure, diabetes... etc), duration of catheterization (more than 7 days) and duration of ICU stay (more than 3 days).

Sample collection
Urine samples were collected through clamping the catheter till the patient senses the urge to urinate or the bladder becomes palpable. The catheter port was cleaned with 70% alcohol and then 10 ml urine withdrawn using a needle and syringe.

The samples were cultured using semiquantitative methods on CLED agar via standard loop method. Also, the samples were spread over blood agar and MacConkey’s agar plates. All plates were incubated overnight at 37°C.

Identification
The organisms were identified according to the colony characteristics and biochemical reactions. API 20 E and API 20NE system (bioMerieux, Marcy l’Etoile, France) were used to identify Gram negative isolates, while culture characteristics, catalase and coagulase activity were employed to confirm Gram-positive organisms identity. Simultaneously, a Gram stained smear was also prepared. In addition, germ tube test was done to differentiate Candida albicans from non albicans Candida.

Nosocomial infections were defined as ICU-acquired if an infection was not present or incubating at the time of the patient's admission to the ICU but became apparent during ICU stay (after 48 hours of admission) or within 48 h after transfer from ICU.

Significant Bacteriuria in catheterized patients was defined as colony count of more than $10^3$ colony forming units (CFU) per ml and no more than two bacterial species. While urosepsis was defined as sepsis in the setting of a UTI with a concomitantly positive blood culture with the same organism within 48-hour period (9)

Antibiotic susceptibility testing
Antibiotic susceptibility to Pencillin, Ampicillin, Sulbactam-ampicillin, Piperacillin, Aztreonam, Meropenem, Vancomycin, Cefradin, Cefuroxime, Cefotaxime, Ceftazidime, Ciprofloxacin, Norfloxacin, Trimethoprim-sulfamethoxazole, Gentamicin, and Amikacin was determined using the Kirby-Bauer method and the results were interpreted as per National Committee for Clinical Laboratory Standards (NCCLS) guidelines. (10)

Investigation of detected Enterbacter cloacae outbreak.
Swabs were taken at the time of the E. cloacae outbreak (May 2010) from frequently touched items or surfaces with suspected transmission and from hands of health care workers dealing with the outbreak cases then cultured on MacConkeys plate and incubated at 37°C overnight.

DNA of E. cloacae strains was isolated according to the method described by Lema et al. (11) Subsequently, inter-repeat PCR was performed using the Enterobacterial Repetitive Intergenic Consensus (ERIC) 2-primer (sequence: 5’ AAGTAA GTG ACT GGG GTG AGCG 3’). It was carried out with the following cycling programme: an initial denaturation (5 min, 94°C), followed by 40 cycles of denaturation (1 min, 94°C), annealing (1 min, 36°C) and extension (2 min, 72°C). PCR products were electrophoresed according to standard protocols. (12)
Statistical analysis:
The demographic, clinical, and technical data were collected using a ‘data collection form’ and entered into a computerized database before statistical analysis. Continuous variables were compared using analysis of variance for repeated measures. P-value less than 0.05 were considered statistically significant. All data were expressed as mean ± standard deviation (SD) or patient’s number (n) and percentage (%) as appropriate.

RESULTS

NUTI was confirmed in 81 out of 396 patients (20.5%). As regard CAUTI, all infected patients had a urinary catheter in place during their entire stay, therefore all NUTI were CAUTI. The mean age for all patients was 59.39±14.9 years. The median age was 60 years (11-89) with male to female ratio (0.9:1.03). Average days of catheter in-situ were 4.16 days per patient (4-12 days). Average duration of stay in the Neurological ICU was 4.1 days per patient (4-18 days).

Thirty patients in age group below 40 years old, 274 patients in age group from 40 to 70 years old and 92 patients above 70 years old were admitted in NICU. A gender difference (female showed more frequency of NUTI) was statistically significant. Twelve out of seventeen immunocompromised patients developed NUTI. The immuno-compromised group showed a higher incidence of NUTI.

Seventy six patients with catheter in-situ for more than seven days developed CAUTI as compared to five with catheter in-situ for less than seven days. The difference was highly statistically significant (’p’ <0.05). There was a higher risk of acquiring NUTI in patients with more than three days of stay in NICU (’p’ <0.05). Ninety four out of 396 patients died (mortality-23.7%). 19 out of 81 patients with NUTI died (23.5%) and 73 out of 315 patients without NUTI died (23.2%). The mortality was not significantly higher among all groups.

The organisms that caused NUTI were Escherichia coli (E.coli) (24) 27.3%, Klebsiella pneumonia (K. pneumoniae) (16) 18.2%, Pseudomonas aeruginosa (P.aeruginosa)(12) 13.6%, Enterobacter cloae (9) 10.2%, Candida albicans (9) 13.6%, Proteus spp. (8) 9.1%, methicillin resistant Staphylococcus aureus (MRSA) (5) 5.7%, Coagulase negative Staphylococci (2) 2.27%, Staphylococcus aureus (3) 3.4%. Single organism infection happened in 74 (80.7%) cases and mixed bacterial species in 7 cases (19.3 %.). Eight patients (9.9%) had the same isolates (2MRSA, 2 Pseudomonas, 2 Enterobacter, 1 E.coli and 1 Klebsiella) and concomitantly isolated from blood and urine samples. Four cases were saved while the other 4 sadly died.

E. coli and Proteus that were isolated from urine samples through the catheter were most susceptible to amikacin at a percentage of (83.3%) and (87.5%) respectively. Meropenem was the second most effective antibiotic against both isolates at a percentage of 70.8% and 75% respectively. While Pseudomonas was susceptible to norfloxacin and ciprofloxacin (91.7%) followed by ceftazidime (75%) and meropenem (66.7%).

Klebsiella isolates were mostly sensitive to meropenem (93.4%) followed by nitrofurantoin (81.3%), amikacin (68.7%) and gentamicin (43.8%). Enterobacter isolates showed best sensitivity to meropenem(100%) followed by ciprofloxacin (88.9%). Staphylococcus aureus, MRSA and CoNS shared 100% sensitivity to vancomycin. [Table -1]

For the period of one month (May 2010) of the current study, 3 patients developed Enterbacter cloae UTI. The isolates had the same antibiotic susceptibility pattern. The isolates revealed resistance to pencillins, aminoglycosides and second and third generation cephalosporins, while all showed 100% sensitivity to meropenem.

When they were typed using ERIC, Interrepeat PCR showed the same genotype that was yielded in the 3isolates and the hands of one nurse. These data denoted that this nurse was a vector of transmission. (Figure- 1)

Interventions

Sticking to hand cleansing, especially hand disinfection was strongly reinforced. Also isolation of infected patients, disinfection of environmental sources and reduction of consumption of empirical antibiotics e.g. meropenem, gentamicin and ceftazidime were done.
Table (1) Antibiotic sensitivity Pattern of the isolated bacteria

<table>
<thead>
<tr>
<th>Antibiotics*</th>
<th>K. pneumoniae n = 16</th>
<th>S. aureus n = 3</th>
<th>E. coli n = 24</th>
<th>P. aeruginoa n = 12</th>
<th>CONS n = 2</th>
<th>MRSA n = 5</th>
<th>Proteus spp. n = 8</th>
<th>E. cloacae n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin(10)</td>
<td>S-R</td>
<td>S-R</td>
<td>S-R</td>
<td>S-R</td>
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<td>S-R</td>
<td>S-R</td>
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</tr>
<tr>
<td>Ampicillin(10)</td>
<td>0-16</td>
<td>1-2</td>
<td>6-18</td>
<td>1-1</td>
<td>1-1</td>
<td>0-5</td>
<td>0-8</td>
<td>0-9</td>
</tr>
<tr>
<td>Amp/Sulbactam(20)</td>
<td>3-13</td>
<td>2-1</td>
<td>5-19</td>
<td>1-1</td>
<td>1-1</td>
<td>0-5</td>
<td>0-8</td>
<td>0-9</td>
</tr>
<tr>
<td>Meropenem(10)</td>
<td>15-1</td>
<td>2-1</td>
<td>17-7</td>
<td>8-4</td>
<td>2-0</td>
<td>1-4</td>
<td>5-3</td>
<td>9-0</td>
</tr>
<tr>
<td>Aztreonam(30)</td>
<td>6-10</td>
<td>1-4</td>
<td>14-10</td>
<td>7-5</td>
<td>1-1</td>
<td>0-5</td>
<td>5-3</td>
<td>0-9</td>
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<tr>
<td>Piperacillin(100)</td>
<td>- -</td>
<td>- -</td>
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<td>- -</td>
<td>7-5</td>
<td>- -</td>
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<tr>
<td>Amikacin(30)</td>
<td>11-5</td>
<td>1-4</td>
<td>7-8</td>
<td>1-1</td>
<td>1-4</td>
<td>1-7</td>
<td>1-9</td>
<td>0-9</td>
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<tr>
<td>Gentamycin(10)</td>
<td>7-9</td>
<td>- -</td>
<td>16-8</td>
<td>4-8</td>
<td>- -</td>
<td>0-5</td>
<td>5-3</td>
<td>0-9</td>
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<tr>
<td>Cefradin (30)</td>
<td>0-16</td>
<td>2-1</td>
<td>6-18</td>
<td>- -</td>
<td>1-1</td>
<td>1-4</td>
<td>1-7</td>
<td>0-9</td>
</tr>
<tr>
<td>Cefuroxime (30)</td>
<td>0-16</td>
<td>2-1</td>
<td>17-7</td>
<td>- -</td>
<td>2-0</td>
<td>1-4</td>
<td>2-6</td>
<td>0-9</td>
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<tr>
<td>Cefotaxime(30)</td>
<td>4-12</td>
<td>0-3</td>
<td>11-13</td>
<td>3-9</td>
<td>2-0</td>
<td>2-3</td>
<td>3-5</td>
<td>1-8</td>
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<tr>
<td>Cefazadime(30)</td>
<td>5-11</td>
<td>0-3</td>
<td>11-13</td>
<td>9-3</td>
<td>2-0</td>
<td>1-4</td>
<td>2-6</td>
<td>2-7</td>
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<tr>
<td>Vancomycin(30)</td>
<td>- -</td>
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<td>2-0</td>
<td>5-0</td>
<td>- -</td>
<td>- -</td>
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<tr>
<td>Ciprofloxacin(5)</td>
<td>8-8</td>
<td>2-1</td>
<td>14-10</td>
<td>11-1</td>
<td>1-1</td>
<td>1-4</td>
<td>6-2</td>
<td>8-1</td>
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<td>Norfloxacin(10)</td>
<td>12-4</td>
<td>2-1</td>
<td>13-11</td>
<td>11-1</td>
<td>1-1</td>
<td>1-4</td>
<td>7-1</td>
<td>7-2</td>
</tr>
<tr>
<td>Nitrofurantoin (300)</td>
<td>13-3</td>
<td>2-1</td>
<td>13-11</td>
<td>0-12</td>
<td>1-1</td>
<td>0-5</td>
<td>2-6</td>
<td>6-3</td>
</tr>
<tr>
<td>Trimethoprim and sulphamethoxazole (1.2/23µg)</td>
<td>10-6</td>
<td>1-2</td>
<td>14-10</td>
<td>- -</td>
<td>0-1</td>
<td>0-5</td>
<td>5-3</td>
<td>3-4</td>
</tr>
</tbody>
</table>

*S: sensitive, R: resistant, * concentration expressed as µg per disc

Figure (1): Representative ERIC-PCR amplification. Lane 1 is the 10000bp DNA ladder (200,400,600,300,400,800,1000,1500,800,2000,2500,3000,4000,5000,6000,8000 and10000bp.) Lane 3, 4 and 6 represent E. cloacae outbreak isolates. Lane 8 shows E. cloacae from the hands of the source.
DISCUSSION

Health care associated UTI, especially when catheter related, can occur either by the endogenous or exogenous routes. In the later cross-transmission of uropathogens plays key role. This is a very multifaceted issue, encompassing hygiene, cross-transmission, urinary catheter, host immunity, antibiotic therapy and emergence of antibiotic resistance.(13)

In the current study, we investigated the frequency of NUTI in patients of a neurological ICU. NUTI was seen in 81 out of 396 patients (20.5%).(9,12,14,15) While in 2 studies from Germany, urinary tract infections (4.2% and 8.7%) were reported at a much lower rate.(4,16) Also urinary tract infections reported from an Iranian study at a rate of 43.2%.(1) The relative high incidence in present study may be owed to the insufficient level of care in our neurology ICU.

E. coli (27.3%) was the commonest organisms isolated from urine collected through the catheter. This result is analogous to other quoted data (3,13,17,18,19,20,21) while not running with the findings of other authors. (8,22) As regard antibiotic susceptibility, amikacin was more potent against E.-coli and Proteus than other Gram negative organisms while meropenem appeared to be the most effective against Klebsiella and Enterbacter. Ciprofloxacin was mostly effective against Pseudomonas while all isolated Staphylococci were susceptible to vancomycin.

Aforementioned data are so beneficial for tailoring empirical antibiotic therapy. Since NUTI are resulted from a diversity of Gram-negative as well Gram-positive bacteria, which may sway from time to time and from one institution to the other. No antibacterial agent would be appropriate for all clinical location; therefore each institution must have its own recent information available. (13)

The present results revealed eight patients (9.9%) had the same organism (2MRSA, 2 Pseudomonas, 2 Enterobacter, 1 E. coli, and 1 Klebsiella) isolated from the culture of urine collected through the catheter and the blood culture. Savas et al., stated that urosepsis developed in 6% of the cases although Laupland et al., confirmed urosepsis in 1.37% of ICU-acquired UTIs that showed simultaneous positive blood culture with the same organism.(19,20) The discrepancy in results could be explained by the difference in the study population.

Meanwhile, Rosser et al demonstrated higher occurrence rate (15.8%). (20) Dissimilarly, no case of catheter related sepsis was detected in the study of Tullu et al. (9) obviously urosepsis, carried high mortality rate (50%).(1,9,19,24,25) Old age, female sex and immunocompromised status showed increased risk of NUTI in present study. These results was concurred with the results of other published data which documented a higher risk for developing bacteriuria in adult female patients, the elderly and critically ill patients with a urinary catheter. (2,19,26,27,28,29,30) Although the study of Tullu et al which carried in pediatric ICU showed these factors is not considered as risk factor at all. (9) This disparity could be clarified by different studied age groups.

According to the collected data, it was deduced that the most significant risk of acquiring NUTI in patients was prolonged catheterization.(2,8,19,31) Mulhall et al showed that the number of days of the urinary catheter in-situ was a significant factor in acquiring catheter related infection. (32) Garibaldi et al have shown the risk of bacteriuria in indwelling urinary catheters to be 8.1% for each day the catheter remains in-situ. (26)

The prolonged hospitalization in the NICU more than 3 days had higher risk of acquiring NUTI (‘p’ value =0.01). The extended hospital stay increases the colonization of skin and environment of the patient that may be responsible for higher incidence of NUTI.(1,3)

NICU-mortality rate could be recurred to the underlying critical conditions of the patients rather than the presence of urinary catheter as no statistical significance was detected between those with urinary tract infections and those without regarding mortality. The current result is much comparable to the result of Tullu et al who recorded 29.5% mortality rate. (9) While, mortality rate in Neurological ICU in Turkey in patients with UTI was 62.5%. (1)

There was outbreak of Enterobacter cloacae NUTI. It was emerged as 3 cases with the same antibiotic susceptibility pattern. Molecular typing confirmed the entire isolates of the same clone. Surveillance cultures incriminated the hands of a nurse as a source of infection. These results confirmed that many single-clone outbreaks could be resulted from cross-transmission via healthcare workers (HCWs). (9)
Furthermore over-crowding and understaffing with increased workload in the period of E. cloacae outbreak have also been identified as auxiliary causes. (33)

These issues raised the infection rate because of slippage of healthcare worker aseptic technique or inadequate hand washing which gave us an idea about hygienic means that were away from being optimal. (32)

An explanation which makes sense for outbreaks spread in hospitals is that nosocomial pathogens seemed to be apt for selection. Thus, in a nosocomial milieu, selection of certain bacterial clones occur leading to a shrinking of bacterial diversity for the sake of nosocomial pathogens, which may then spill over even to the community too. Hence, cross-infection always plays a key role in this selective process. (8)

However, Studies using different typing methods have ended in that horizontal transmission occurs rarely. As nosocomial infections with E. cloacae caused by its outgrowth from the patient’s endogenous gut microbiota aided by the utilization of antibiotics. Yet, more recent molecular studies signified that cross-infection may occur more frequently than had been implicated. (33)

It is well known that Enterobacter strains isolated from hospitalized patients, particularly those in intensive care units, are widely resistant to the major groups of antimicrobial agents. The antibiotic resistance profile of the outbreak isolates in current study was resistance to aminoglycosides, all the β-lactam antibiotics tested with the exception of the carbapenem. The isolates were uniformly sensitive to carbapenem as well as the quinolone. (32)

It was verified that reinforcement of hygiene practices especially hand hygiene, the use of proper disinfection procedures, restrictions of antibiotic use and limitation of new admissions, led to control of the outbreak. (34)

We concluded that nosocomial urinary tract infections were common in patients in neurological ICU. E. coli was the commonest infecting organism in present study. Furthermore, prolonged catheterization and hospital stay were the two most important risk factors that increase the incidence of NUTI.

Also, it seems reasonable that application of rigorous infection control measures considering cost effectiveness had a great impact on reduction of nosocomial infection, limitation of the emergence of antibiotic resistant organisms and management of detected outbreak.

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عدوى التهاب القناة البولية المكتسب العارضي بوحدة العناية المركزية للأمراض العصبية:

تتسبب عدوى التهاب القناة البولية في المستشفيات في زيادة معدلات وفيات الإصابات المرضية وارتفاع نسبة الوفيات في وحدات العناية المركزية. وقد أجريت هذه الدراسة المستقبيلة لتحديد نسبة الإصابات بعɗوى التهاب القناة البولية والМИتكوينات المتّشرة بالإضافة إلى العوامل المعرضة للأصابات في وحدة العناية المركزية للأمراض العصبية بالمستشفي الجامعي بالاصرورة.

أجريت هذه الدراسة العائليين في وحدة العناية المركزية لمدة تزيد على 80 ساعة من أغسطس 2009 الى سبتمبر 2010. تم تشخيص عدوى المستشفيات وفقًا لقواعد مركز الوقاية من الأمراض ومكافحتها. تم دراسة العوامل المعرضة مثل السن ووقت البقاء بالمستشفى والمسافات البولية ونوع المناعة واحتياطات الوقاية. كما تم عزل الميكروبات وتعريفها بالإضافة إلى دراسة حساسيتها للمضادات الحيوية. أثناء الدراسة تم تشخيص جناح ميكروب الإنتروليلوكار مسببًا التهاب القناة البولية و استخدمت طرق البيولوجيا الجزيئية لتفعيل الميكروب وتحديد مصدره.

كانت نسبة إصابة المرضى 0.5% و ارتفعت نسبة الإصابات في كبار السن ومرضى نقص المناعة والمصابين بمرض الأيدز. كان أكثر الميكروبات عزلًا هو ميكروب إسمارباتيا الفولون. كان عقار الإيميسيل مساعدًا في التخلص من الميكروبات الحيوية ففعالة ضد هذه الميكروبات. وجد المرضى أن معالجة العدوى الناتجة مبتدئًا لظهور الميكروبات المقاومة للمضادات الحيوية وانخفاض الجانحة للمصابة في وحدات العناية المركزية.