INFECTIONS IN NOTES

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Introduction of NOTES was welcomed with great enthusiasm. Several experimental and human studies proved feasibility and safety of NOTES procedures (1). In some applications it might be a valid option, however it seems it will not devalue most of well established laparoscopic and open procedures (2). In terms of surgical safety, one of the serious unknowns of NOTES are surgical infections. There is little known about the prophylactics, epidemiology and potential treatment of infections after NOTES procedures. The number of studies assessing this issue is limited. Some data can be extrapolated from other non-NOTES procedures performed through the same access sites. Both open and laparoscopic surgeries start with incision of the skin, which is quite simple to decontaminate. NOTES starts with mucosal incision inside the vagina, stomach or large bowel and all mucosa host numerous populations of microorganisms (stable and transient flora), which can contaminate peritoneal cavity or even translocate to blood (3). From the microbiological point of view surgical procedures are always related to transmission of flora to their non-physiological sites. Therefore antibiotic prophylaxis with or without other preventive measures seems to be essential in all cases. Surgical accesses are microbiologically very similar, and vary in possible magnitude of microbial transmission. Additionally since there is no open wound and external drainage is limited, surgical site infections in NOTES are to be much harder to diagnose and treat.

Endoscopic equipment

The most obvious measure to prevent exogenous infection (not only bacterial but also fungal and viral) in NOTES is by using highly disinfected endoscopes (4, 5). In most of the described traditional endoscope-related cases of transmission of infection, a breach in currently accepted guidelines of cleaning and disinfection was identified. Similar problems can be encountered in NOTES procedures utilizing flexible endoscopes. These include:

- procedural errors in cleaning and disinfection of the endoscope or its accessories, resulting in inadequately disinfected devices;
- insufficient exposure of the endoscope to a currently approved liquid chemical sterilizing solution/disinfectant or the use of a substandard disinfectant solution;
- contaminated water bottles and irrigating solutions;
- improper use of or inadequately designed (contaminated) automated endoscope repro cessors; and
- inadequate drying of endoscope channels (particularly the elevator channels of duodenoscopes) before storage (4).

Contamination of endoscopes in NOTES procedures was presented by Narula et al. where positive cultures were reported after disinfection of the gastroscopy channels (6).

In response to those problems EURO-NOTES working group made following recommendations:
1. High-level disinfection is mandatory for endoscopes used for NOTES but sterilization with ethylene oxide is not necessarily required. Automated cleaning of all channels should be guaranteed.

2. Sterility is mandatory for all disposable accessories, also sterile water should be used for irrigation.

3. Operators should be in surgical attire and an ideal site or the procedure is an operating room (8).

Antibiotic prophylaxis

Currently no NOTES-specific guidelines or recommendations for antibiotic prophylaxis are available. According to EURO-NOTES 2010 prolonged perioperative therapy with an antibiotic should be procedure related, but antibiotic lavage of the entry point is not necessary (8).

Therefore it seems justified to follow the well established guidelines for classical surgical prophylactic antibiotics. The latest Sanford Guide to Antimicrobial Therapy recommends cephalosporines in gastrointestinal and gynecologic surgery: cefazolin or cefoxitin or cefotetan or ceftriaxone or cefuroxime 1.5 g IV as a single dose 30 min before surgery. During a prolonged procedure (≥3 h) it is recommended to add a second dose intraoperatively (9). In colorectal surgery cefazolin 1-2 g IV with metronidazole 0.5 g IV is recommended (alternatively cefoxitin 1-2 g IV, cefotetan 1-2 g IV, ampicillin-sulbactam 3 g IV or ertapenem 1 g IV).

The above mentioned standard prophylactic antibiotics successfully minimize incidence of postoperative infections in non-NOTES surgery (9). It is not necessary for the antimicrobial agent used for prophylaxis to cover each and every possible pathogen (10). As with all surgical interventions NOTES will not be completely free of infectious complications. However human reports are encouraging since no infectious complications have been described despite bacterial contamination of peritoneum.

Access route

Kantsevoy specified three different types of contamination during NOTES: 1) contamination of the sterile endoscope during passage through the natural orifice, 2) leakage of the access organ’s content into peritoneum during the procedure, 3) contamination by the targeted intraperitoneal organ like gall-bladder (11). Apart from peritoneal contamination through poorly sealed transluminal access site it can also spread through hematogenous route. Therefore Kantsevoy advocates maximally aseptic conditions during NOTES, especially the early days of its use in humans (11). Also Wagh et al. in the early days of NOTES prioritizes a policy of zero or low-tolerance for complications that are unique to the method (e.g. peritoneal infection, bleeding and damage to surrounding structures related to gastrotomy and its closure) (12).

Different NOTES accesses pose different infection risk due to characteristic flora and are discussed below.

Transvaginal

This access has a long history dating the early 19th century with the advent of culdoscopy (13). In 1960s and 1970s it was widely used for diagnostic and therapeutic procedures. Nowadays there are many reports of its modifications such as transvaginal laparoscopy or culdolaparoscopy. In these procedures the infection rate is very low ranging between 0.3% to 1% (13). Also transvaginal approach is the most commonly used access point for NOTES procedures, and is connected with very low rate of infectious complications (hybrid transvaginal cholecystectomy – 0.3% pouch of Douglas abscess, 0.3% wound infection) (14). German prospective NOTES registry reported 1% infectious complications like urinary tract infection, wound infection, vaginal mycosis and bacterial vaginitis in transvaginal cholecystectomy (28). Tsin et al. used cephalosporins and metronidazol as antibiotic prophylaxis and cleaned vagina with 10% povidone iodine in 100 minilaparoscopy-assisted natural orifice surgeries and no infectious complications emerged (15). Linke et al. who studied microbial contamination during transvaginal cholecystectomy reported no growth of microorganisms in nearly 60% patients (16). An ongoing infection should be a temporary contraindication to NOTES. Vaginal flora
is very complex and in case of vaginitis or sexually transmitted diseases could be even more diversified (3). Common encountered aerobic facultative pathogens are Escherichia coli, Enterococcus faecalis and Candida albicans. The presence of mycoplasma like Mycoplasma hominis or Ureaplasma urealyticum which are resistant to all beta-lactams (no cellular wall) should be kept in mind when treating a suspected postoperative infection after a transvaginal access. In cases like this doxycycline or fluoroquinolone (moxifloxacine or ofloxacine) can be used for treatment (3, 9). In most cases of infection of any sort, multiple bacterial species are involved, including both aerobic and anaerobic organisms. In many cases, clinical health will be restored even if the antibiotic treatment covered some but not all of the bacteria present in the infected area. Since it is extremely costly and time-consuming to culture all anaerobic bacteria, these studies are generally not undertaken, and therapy must be selected before culture results are available in the great majority of cases (10).

Transgastric

Transgastric access is second most widely reported in NOTES (16). It was used by endoscopists for many procedures, such as PEG placement or drainage of pancreatic cysts (5). Manipulation of the endoscope and multiple re-entry into peritoneal space may cause the stomach to rotate and spill gastric contents – potentially contaminating sterile field (17). In experimental animals Kim and Kalloo observed microabcesses after such leaks (5). Merrifield’s report – cases of bacterial peritonitis after transgastric organ resections in pigs – lead to conclusion in NOSCAR consensus, that no level of leak rate from gastric incision is acceptable (2, 18). Endoscopy studies reported different rates of bacteremia ranging from 0.5% to 22.8% depending on the procedure (4). Although the bacteremia were transient and asymptomatic with unclear clinical relevance, it has to be remembered, that in patients with certain risk factors bacteremia can result in endocarditis or even sepsis (4). Therefore it will be of great interest to execute similar microbiologic experiments in NOTES and perform blood cultures together with peritoneal fluid or gastric fluid cultures. Most predominant bacteria are enteric rods like Escherichia coli and enterococci. In case of previous hospital stay and antimicrobial therapy patients may be colonised by Pseudomonas aeruginosa, Acinetobacter baumannii and other potentially multi-antibiotic resistant pathogens (3). Although stomach is relatively less colonized with microorganisms comparing to other NOTES access sites, in early human applications of NOTES, its irrigations with antibiotics or topical disinfectants like povidone iodine were used for oral cavity and/or gastric lavage (5, 19). The effect of this prophylactic antibiotic irrigation is not yet clear and may be debatable. Narula et al. used only IV perioperative antibiotics without stomach irrigation and reported no infection related to detected bacterial contamination of the peritoneum (6, 7).

To minimize the transmission of oral bacteria to peritoneal cavity with the endoscope an overtube device can be used (5). On the other hand it was found that intrinsic sterility of the scope does not pose an infectious risk and the act of passing the endoscope through non sterile oropharynx and stomach out into the peritoneal cavity does not expose the patient to a clinically significant increased risk of infection. (20). Moreover Nau et al. found that in 23% of the cases cross-contamination occurred but no infectious complications in 40 patients cohort were observed. (20). It is also of great interest the influence of PPI therapy and existing Helicobacter pylori (HP) colonisation on bacterial growth in stomach and the increased risk of infection. In Sanduleanu et al. study in patients taking proton pump inhibitors, both luminal and mucosal growth of non-H. pylori bacteria was significantly greater in HP (+) than HP (-). Luminal growth of non-H. pylori flora increased with the intragastric pH level, whilst mucosal bacterial growth increased with the duration of acid inhibition. Non-H. pylori flora not only contaminated the gastric fluid but also colonized the gastric mucosa of a large proportion of patients treated long-term with acid inhibition (20, 21). Narula et al. reported increased bacterial contamination of peritoneal cavity after transgastric instrumentation in patients on PPI without subsequent clinically significant infection (7). There was no correlation between the bacterial load within the stomach and the extent of peritoneal contamination (20).

Serious drawback of NOTES studies, which estimated the peritoneal cavity contamination,
was long time from collection to inoculation. As this is the crucial step to ensure bacterial viability and quantity in the sample, future studies should ensure ≤2 hours for specimen transportation (7, 3).

Transcolonic

This access is related with the greatest risk of infection due to dissemination of colonic flora into the surgical field (8). In the absence of preexisting abdominal infection and if the surgical procedure is carried out with skilled technique, colorectal operations are considered clean-contaminated procedures. Bowel-preparation protocol removes most stool from the colon before the procedure but the environment is still highly contaminated (4). The microorganisms isolated most commonly are anaerobes such as the Bacteroides fragilis group and Bifidobacterium spp. These are more common than the aerobes (Enterobacteriaceae:Escherichia coli, Enterococcus spp) and yeasts – Candida albicans (22). In case of infection post transcolonic intervention multiple bacterial species are usually involved. Since it is time-consuming to culture the mixture of all anaerobic and aerobic bacteria, therapy must be selected before culture results are available in the great majority of cases (10). Grant et al. reported that culturing ≥4 different microorganisms from peritoneal fluid during colorectal surgery correlated with postoperative infection. Based on this finding he suggested that future studies should reexamine the time of perioperative antibiotics by performing qualitative and quantitative operative site bacteriology (23). Endoscopic procedures such as sigmoidoscopy and colonoscopy are associated with 0.5% and 2.2% bacteremia, respectively (4). In lower- as with upper-gastrointestinal endoscopic procedures isolated bacteria are quite the same, bacteremia is usually transient and asymptomatic. Cases of endocarditis following flexible sigmoidoscopy or colonoscopy have been reported (4). Mechanical bowel preparation technique for colorectal surgery according to Sanford Guide consists of 2-4 L polyethylene glycol electrolyte solution po over 2 h the day before procedure, clear liquid diet only, three times a day neomycin 1g plus erythromycin base 1 g po and nil per os after midnight on the day of the procedure (9). Perioperative parenteral antibiotic prophylaxis regimens were given above. The role of mechanical bowel preparations has been questioned in colorectal surgery and transcolonic access in NOTES seems to furtherly complicate the use and extent of this method.

Transurethral/transvesical

Transvesical access offers an interesting supplement to the above mentioned approaches. In physiological state urinary bladder is not colonized by bacteria. Endourologic procedure like transurethretal prostatectomy (TURP) benefited with the use of antimicrobial prophylaxis by decreased bacteriuria to 9,1% and clinical septicemia to 0,7% (24). Transvesical incision would effectively be the best access site for NOTES with its low rate of peritoneal contamination (24). Yamamoto et al. underlined that patients undergoing TURP should have urine sterile at the operation. The same approach toward sterile urine should be followed in this early days of NOTES. Most common pathogens causing infections in the urinary tract are Escherichia coli, Proteus mirabilis, other enterobacteria and enterococci followed by Candida albicans (3). Antibiotics recommended for urological prophylaxis are the same as for other surgical operations being penicillins with beta-lactamase inhibitor, or first- or second-generation cephalosporins (24). A study by McGee examined the microbial contamination of the human peritoneum after transvesical incision and exposure of the peritoneal cavity to bladder contents during robot-assisted laparoscopic prostatectomy (RALP) (25). Intraoperatively peritoneal fluid was collected for cultures and aerobes were detected only in 5 of 60 patients with no clinical signs of infection. However this study might have overestimated bacterial contamination via the bladder during RALP, by not differentiating bladder bacteria from those originated from the seminal or prostatic fluid during prostatectomy.

SUMMARY

After the phase of animal research NOTES procedures were successfully introduced to human studies. Overall complication count, mainly because of technical problems, is still
relatively high but in well prepared patients (proper preparation of entry site, antibiotic prophylaxis) risk of infection is below 1%. Douglas pouch abscesses and entry site wound infection were described after transvaginal approach. Peritonitis and sepsis were reported (in animals) mainly after transgastric approach complicated by leak of gastric fluid to peritoneal cavity from unsealed closure of entry site and in cases operated without antibiotic prophylaxis (26).

CONCLUSIONS

Concluding NOTES has relatively low infectious complication rate when proper perioperative and operative protocol is used including aseptic procedures, antibiotic prophylaxis and leak proof sealing of entry site. More microbiology focused studies should be designed. Technological development and procedure standardization seem mandatory before NOTES becomes a safe and accepted procedure.

REFERENCES


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