

RATIONAL USE OF ANTIBIOTICS AND ANTIBIOTICS PROPHYLAXIS IN UROLOGICAL PRACTICE

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Antibiotic resistance has become a global phenomenon nowadays, particularly affecting the developing nations where medical rules & regulations are not strictly followed. Countries like Bangladesh are witnessing some of the grave effects of this hard-nut-cracking problem. In recent times, the number of patients diagnosed with antibiotic resistance is increasing at an alarming rate. Not only is it posing a great challenge to the scientists to find a new cure but also putting the future of the world at stake. Superbugs like MRSA, Carbapenem-Resistant Enterobacteriaceae (CRE),

Multidrug-Resistant Acinetobacter or Neisseria gonorrhoeae are giving us a red signal about our health sector in the coming days.

The rapid pace of antibiotic resistance is occurring due to so many factors, however, needless to say, that a very large portion of it is happening owing to our lack of knowledge and understanding of microbes, antibiotics, and resistance.

This article is, aimed to draw your attention to the science behind it in a simple manner and provide the reader with a basic concept of what antibiotics are, how they become resistant and what are the possible solutions to go for. I begin this article by defining what microbes & antibiotics are, how they are connected and then move on to explaining how resistance occurs against antibiotics and later come its possible solutions.

Inappropriate use of antibiotics is rampant in South East Asia[1,2]and is a major contributor to antimicrobial resistance.[3, 4] However, data on antibiotic use are scant, few effective interventions to improve appropriate antibiotic use have been implemented[5,6], and implementation of policies for appropriate use of antibiotics is also poor[7].

Effective policies included having a government health department to promote rational use of medicines, a national strategy to contain antimicrobial resistance, a

national drug information centre, drug and therapeutic committees in more than half of all general hospitals and provinces, and undergraduate education on standard treatment guidelines. An updated essential medicines list and national formularies were also associated with lower antibiotic use[8].

Since 2010, South East Asian countries have been conducting national situational analyses on medicines management every four years,[9]supported by the World Health Organization. This process involves rapid systematic data collection on use and availability of medicines, including antibiotics, and implementation of policies to ensure appropriate use[10].

Overuse and misuse have contributed to the growing problem of resistance amongst uro pathogenic bacteria is a serious threat to public health. In acute care hospitals, 20-50% of prescribed antibiotics are either unnecessary or inappropriate [11]. In response, a worldwide initiative seeks to incorporate Antimicrobial Stewardship programs in healthcare [12]. Antimicrobial Stewardship aims to optimise clinical outcomes and ensure cost-effective therapy whilst minimising unintended consequences of antimicrobial use such as healthcare associated infections including *Clostridium difficile*, toxicity, selection of virulent organisms and emergence of resistant bacterial strains [12].

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Stewardship programs have two main sets of actions. The first set mandates use of recommended care at the patient level conforming to guidelines. The second set describes strategies to achieve adherence to the mandated guidance. These include persuasive actions

such as education and feedback together with restricting availability linked to local formularies.

Urinary tract infection (UTI) is the most common indication for antimicrobial use in hospitals and a significant proportion of this use is inappropriate or unnecessary. The Antimicrobial Stewardship Program at the Nebraska Medical Center has developed guidelines to facilitate the evaluation and treatment of UTIs. Ordering of Urine Culture: Urine cultures should only be obtained when a significant suspicion for a UTI exists based on patient symptoms. Urine culture data should always be interpreted taking into account the results of the urinalysis and patient symptoms. In the urinalysis the presence of leukocyte esterase suggests WBC will be present while nitrites suggest that gram-negative organisms are present. Neither of these findings is diagnostic of a UTI. Indication for urine culture: When signs or symptoms suggest a urinary tract infection is present (see below) In patients who cannot provide history (intubated, demented) and have sepsis without another source to explain it

Urine culture NOT recommended: Change in urine color, odor, or turbidity these are typically due to patient hydration and not indicators of infection Patient lacks symptoms of UTI Automatically in workup of fever or sepsis patients who can provide a history should not have a urine culture obtained as part of fever evaluation unless symptoms suggest a UTI is present. Pre-operatively except in urologic surgery where mucosal bleeding is anticipated. When a urinary catheter is placed or changed at admission after treatment of UTI to document cure

Interpretation of Urine Culture:

Bacteria are frequently noted on urinalysis and cultured from urine specimens. The presence of bacteria in the urine may indicate one of 3 conditions: 1) specimen contamination; 2) urinary tract infection (UTI); or 3) asymptomatic bacteriuria (ASBU). When evaluating the clinical significance of a urine culture these 3 conditions must each be considered and classification should be based upon history and exam findings coupled with urine findings. Specimen contamination should always be considered as this is common, particularly in female patients. High numbers of squamous cells on the urinalysis (>20) suggests contamination and results of the culture should generally be ignored. In patients with a positive urine

culture where no contamination exists, clinicians must determine if the patient is exhibiting symptoms of a UTI.

Symptoms typical of a UTI are urinary frequency or urgency, dysuria, new onset hematuria, suprapubic pain, costovertebral tenderness or fever. Patients with a urinary catheter in place may have more vague symptoms such as new onset or worsening fever, chills, pelvic discomfort, acute hematuria and altered mental status with no other identifiable etiology. It is important to recognize that pyuria is not an indication for treatment. Pyuria is the presence of an increased number of polymorphonuclear leukocytes in the urine (generally >10 WBC/ hpf) and is evidence for genitourinary tract inflammation. Pyuria can be seen in patients with catheter use, sexually transmitted diseases, renal tuberculosis interstitial nephritis or ASBU. The absence of pyuria is a strong indicator that a UTI is not present and is useful in ruling out a UTI.

A Cochrane review of effectiveness of interventions to improve antibiotic prescribing practices for hospital inpatients, updated in 2017, found high-certainty evidence that such interventions are effective in increasing adherence with antibiotic policy leading to reduced antibiotic treatment duration and may also reduce hospital stay. The review found no evidence that reduced antibiotic usage increased mortality [14].

The important components of antimicrobial stewardship programs are : Regular training of staff in best use of antimicrobial agents, adherence to local, national or international guidelines; regular ward visits and consultation with infectious diseases physicians and clinical microbiologists, audit of adherence and treatment outcomes, regular monitoring and feedback to prescribers of their performance and local pathogen resistance profiles[15].

Asymptomatic bacteriuria in adults

Urinary growth of bacteria in an asymptomatic individual (asymptomatic bacteriuria - ABU) is common, and corresponds to a commensal colonization [25]. Clinical studies have shown that ABU may protect against superinfecting symptomatic UTI, thus treatment of ABU should be performed only in cases of proven benefit for the patient to avoid the risk of selecting antimicrobial resistance and eradicating a potentially protective ABU strain [26, 27]. The aim of this section is to support the

clinician in deciding when ABU should or should not be treated. Asymptomatic bacteriuria occurs in an estimated 1-5% of healthy pre-menopausal females. Increasing to 4-19% in otherwise healthy elderly females and men, 0.7-27% in patients with diabetes, 2-10% in pregnant women, 15-50% in institutionalised elderly populations, and in 23-89% in patients with spinal cord injuries [28]. Asymptomatic bacteriuria in younger men is uncommon but, when detected, chronic bacterial prostatitis must be considered. The spectrum of bacteria in ABU is similar to species found in uncomplicated or complicated UTIs, depending on the presence of risk factors.

Asymptomatic bacteriuria in an individual without urinary tract symptoms is defined by a mid-stream sample of urine showing bacterial growth 10^5 cfu/mL in two consecutive samples in women [17] and in one single sample in men [16].

In a single catheterized sample bacterial growth may be as low as 10^2 cfu/mL to be considered representing true bacteriuria in both men and women [18, 19]. Diagnostic work-up should include measurement of residual urine while cystoscopy and/or imaging of the upper urinary tract is not mandatory if the medical history is otherwise without remark. If persistent growth of urease producing bacteria, i.e. *Proteus mirabilis* is detected, stone formation in the urinary tract must be excluded [20]. In men, a digital rectal examination (DRE) has to be performed to investigate the possibility of prostate diseases.

For the subgroups of pregnancy, prior to urologic surgeries, postmenopausal women and institutionalized elderly patients only data from randomized- controlled trials (RCT) were included, on which a meta-analysis was performed [21].

The following patient populations were not covered by the systematic review: immuno-compromised patients; patients with candiduria; patients with dysfunctional and/or reconstructed lower urinary tracts; patients with indwelling catheters[33].

Patients without identified risk factors (Asymptomatic bacteriuria in adults:

Asymptomatic bacteriuria does not cause renal disease or damage [22]. Only one prospective, non-randomised study investigated the effect of treatment of ABU in adult, non-diabetic, non-pregnant women [35], and found no difference in the rate of symptomatic UTIs. Furthermore, as the treatment of ABU has been proven

to be unnecessary in most high-risk patient subgroups, there is panel consensus that the results of these subgroups can also be applied to patients without identified risk factors. Therefore, screening and treatment of ABU is not recommended in patients without risk factors.

Recurrent UTI, otherwise healthy asymptomatic bacteriuria in adults

One RCT investigated the effect of ABU treatment in female patients with recurrent symptomatic UTI and without identified risk factors [23] and demonstrated that treatment of ABU increases the risk for a subsequent symptomatic UTI episode, as compared to non-treated patients (RR 0.28, 95% CI 0.21 to 0.38; 673 patients). This protective effect of spontaneously developed ABU can be used as part of prevention in female patients with recurrent symptomatic UTI. Therefore, treatment of ABU is not recommended. However, occasionally the eradication of a strain considered the causative agent of recurrent episodes of UTI, may be justified.

Pregnant women asymptomatic bacteriuria in adults:

Antibiotic treatment significantly reduced the number of symptomatic UTIs compared to placebo or no treatment [24]. No current literature available but WHO recommends a seven-day antibiotic regimen is recommended for all pregnant women with asymptomatic bacteriuria (ASB) to prevent persistent bacteriuria, preterm birth and low birth weight [25].

Recurrent UTIs

Recurrent UTI: are recurrences of uncomplicated and/or complicated UTIs, with a frequency of at least three UTIs/year or two UTIs in the last six months. Although rUTIs include both lower tract infection (cystitis) and upper tract infection (pyelonephritis), repeated pyelonephritis should prompt consideration of a complicated etiology. Diagnosis of rUTI should be confirmed by urine culture. An extensive routine workup including cystoscopy, imaging, etc. is not routinely recommended as the diagnostic yield is low [122]. However, it should be performed without delay in atypical cases, for example, if renal calculi, outflow obstruction, interstitial cystitis or Urothelial cancer is suspected.

Elderly women have an increased incidence of ABU [26]. Four RCTs compared antibiotic treatment of ABU with placebo controls or no treatment, in a post-menopausal female population, with different antibiotic

doses and regimens, no significant benefit of antibiotic treatment was observed. Therefore, ABU in post-menopausal women does not require treatment, and should be managed as for pre-menopausal women [EAU 2018].

Diabetes mellitus, even when well regulated, is reported to correlate to a higher frequency of ABU [27]. One RCT demonstrated that eradicating ABU did not reduce the risk of symptomatic UTI and infectious complications in patients with diabetes mellitus. The time to first symptomatic episode was also similar in both groups. Furthermore, untreated ABU did not correlate to diabetic nephropathy [28]. Screening and treatment of ABU in well-controlled diabetes mellitus is therefore not recommended. However, poorly regulated diabetes is a risk factor for symptomatic UTI and infectious complications.

Patients with ABU and recurrent UTI, otherwise healthy, treatment of ABU is not recommended. Screening and treatment of ABU is not recommended in patients without risk factors. Screening and treatment of ABU in well-controlled diabetes mellitus is therefore not recommended [29,30].

There were no significant differences in the rate of ABU clearance, graft loss or change in renal function during long-term follow-up up to 24 months [80-83]. Therefore, treatment of ABU is not recommended in renal transplant recipients [31,32].

Patients with indwelling or suprapubic catheters, and nephrostomy tubes, invariably become carriers of ABU, with antibiotic treatment showing no benefit. This is also applicable for patients with ABU and indwelling ureteral stents [33]. Routine treatment of catheter associated bacteriuria is not recommended.

Immuno-compromised and severely diseased patients, patients with candiduria have to be considered individually and the benefit of screening and treatment of ABU should be reviewed in each case. Patients with asymptomatic candiduria may, although not necessarily, have an underlying disorder or defect. Treatment of asymptomatic candiduria is not recommended in patients with an otherwise uncomplicated medical history [34].

Prophylaxis with probiotics (*Lactobacillus* spp). Pooled data from a recent meta-analysis shows no convincing benefit of lactobacillus products as prophylaxis for UTI [36]. However, differences in effectiveness between available preparations suggest further trials are needed

before any definitive recommendation for or against their use can be made.

Studies on prophylaxis with cranberry (a meta-analysis including 24 studies and comprising 4,473 participants showed that cranberry products did not significantly reduce the occurrence of symptomatic UTI for women with UTI [35]. As such no recommendation on the daily consumption of cranberry products can be made.

In procedures entering the urinary tract and breaching the mucosa, particularly in endoscopic urological surgery, bacteriuria is a definite risk factor. The rates of post-operative fever and septicemia were also significantly lower in case of antibiotic treatment compared to no treatment in the two RCTs. One RCT including patients with spinal cord injury undergoing elective endoscopic urological surgeries found no significant difference in the rate of post-operative UTIs between single-dose or 3-5 days short term pre-operative antibiotic treatment of ABU [37].

Uncomplicated pyelonephritis is defined as pyelonephritis limited to non-pregnant, pre-menopausal women with no known relevant urological abnormalities or comorbidities. Pyelonephritis is suggested by fever (> 38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the typical symptoms of cystitis [140]. Without clinical fever diagnosis and treatment of UTI is not recommended.

Complicated UTI (cUTI) occurs in an individual in whom factors related to the host (e.g. underlying diabetes or immunosuppression) or specific anatomical or functional abnormalities related to the urinary tract (e.g. obstruction, incomplete voiding due to detrusor muscle dysfunction) are believed to result in an infection that will be more difficult to eradicate than an uncomplicated infection [38]. Clinical presentation can vary from severe obstructive acute pyelonephritis with imminent urosepsis to a post-operative CA-UTI, which might disappear spontaneously as soon as the catheter is removed. Appropriate management of the urological abnormality or the underlying complicating factor is mandatory. Optimal antimicrobial therapy for cUTI depends on the severity of illness at presentation, as well as local resistance patterns

Urosepsis

Patients with urosepsis should be diagnosed at an early stage. Systemic inflammatory response syndrome (SIRS), characterized by fever or hypothermia, leukocytosis or leukopenia, tachycardia and tachypnea,

has been recognized as a set of alerting symptoms [47,48], however, SIRS is no longer included in the recent terminology of sepsis. Mortality is considerably increased in severe sepsis.

E. coli remains the most prevalent micro-organism. In practices, bacterial strains can be resistant or multi-resistant and therefore difficult to treat [49]. Most commonly, the condition develops in compromised patients (e.g. those with diabetes or immunosuppression), with typical signs of generalized sepsis associated with local signs of infection.

The treatment of urosepsis involves adequate life-supporting care, appropriate and prompt antimicrobial therapy, adjunctive measures and the optimal management of urinary tract disorders. The decompression of any obstruction and drainage of larger infectious abscesses in the urinary tract is essential as first-line focus control [39]. Urologists are recommended to treat patients in collaboration with intensive care and infectious diseases specialists.

Cytokines are involved in the pathogenesis of sepsis syndrome [46]. They are molecules that regulate the amplitude and duration of the host inflammatory response. They are released from various cells including monocytes, macrophages and endothelial cells, in response to various infectious stimuli. The complex balance between pro- and anti-inflammatory responses is modified in severe sepsis. An immunosuppressive phase follows the initial pro-inflammatory mechanism. Sepsis may indicate an immune system that is severely

For diagnosis of systemic symptoms in sepsis either the full Sequential Organ Failure Assessment (SOFA) score, or the quick SOFA score should be applied. Microbiology sampling should be applied to urine, two sets of blood cultures [40], and if appropriate drainage fluids. Imaging investigations, such as sonography and CT-scan should be performed early [41].

Biochemical markers for Urosepsis

Procalcitonin is the inactive pro-peptide of calcitonin. Normally, levels are undetectable in healthy humans. During severe generalised infections (bacterial, parasitic and fungal) with systemic manifestations, procalcitonin levels rise [42]. In contrast, during severe viral infections or inflammatory reactions of non-infectious origin, procalcitonin levels show only a moderate or no increase.

Proadrenomedulline is another sepsis marker. Mid-regional proadrenomedullin has been shown to play a decisive role in the induction of hyperdynamic circulation during the early stages of sepsis and progression to septic shock [43].

Procalcitonin monitoring may be useful in patients likely to develop sepsis and to differentiate from a severe inflammatory status not due to bacterial infection [44]. Serum lactate is a marker of organ dysfunction and is associated with mortality in sepsis [45]. Serum lactate should therefore also be monitored in patients with severe infections.

Treatment of Urosepsis

Fast goal-directed resuscitation was initially shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-Centre study [50]. However, follow up studies in an improved emergency medicine background have not achieved positive effects with this strategy [52-53].

An individual patient data meta-analysis of the later three multicenter trials concluded that early goal-directed therapy did not result in better outcomes than usual care and was associated with higher hospitalization costs [54].

Initial empiric antimicrobial therapy should provide broad antimicrobial coverage against all likely causative pathogens and should be adapted on the basis of culture results, once available [55]. The dosage of the antimicrobial substances is of paramount importance in patients with sepsis syndrome and should generally be high, with the exception of patients in renal failure [55]. Antimicrobials must be administered no later than one hour after clinical assumption of sepsis [55].

Obstruction in the urinary tract is the most frequent urological source of urosepsis. Drainage of obstruction and removal of foreign bodies, such as urinary catheters or stones is therefore the most important source control strategy. These are key components of the strategy. This condition is an absolute emergency.

Urgent adjunctive measures of sepsis are to be immediately organized. Fluid therapy with crystalloids, or albumin, if they are not adequately increasing blood pressure; (passive leg raising resuscitative measures to be adopted. Changes in cardiac output and in arterial pulse pressure are predictors of fluid responsiveness in adults [196].

Vasopressors norepinephrine should be used primarily. Dobutamine is indicated in myocardial dysfunction. Hydrocortisone should be given only if fluid and vasopressors do not achieve a mean arterial pressure of (65 mmHg).

Blood products should be given to target a haemoglobin level of 7-9 g/dl. Mechanical ventilation should be applied with a tidal volume 6 ml/kg and plateau pressure \leq 30 cm H₂O (and a high positive end-expiratory pressure).

Sedation should be given minimally and neuromuscular blocking agents should be avoided; glucose levels should be target at 180 mg/dl. Deep vein thrombosis prevention should be given with low-molecular weight heparin subcutaneously. Stress ulcer prophylaxis should be applied in patients at risk, using proton pump inhibitors. Parenteral nutrition should be started early (< 48 hours).

Early recognition of Urosepsis may decrease the mortality by timely treatment of urinary tract disorders, e.g. obstruction, or urolithiasis. Adequate life-support measures and appropriate antimicrobial treatment provide the best conditions for improving patient survival.

The prevention of sepsis syndrome is dependent on good practice to avoid nosocomial infections and using antimicrobial prophylaxis and therapy in a prudent and well-accepted manner.

Infection control protocol for Specific Urological procedure procedures

Urodynamics

The outcome of clinical UTI was reported in four trials with no benefit found for antibiotic prophylaxis versus placebo [RR (95%CI) 0.73 (0.52-1.03)]. A meta-analysis of nine trials showed that use of antibiotics reduced the rate of post-procedural bacteriuria [RR (95%CI) 0.35 (0.22-0.56)] [56].

Cystoscopy

Low absolute risk of post-procedural UTI, the high number of procedures being performed, and the high risk of contributing to increasing antimicrobial resistance the panel consensus was to strongly recommend not to use antibiotic prophylaxis in patients undergoing flexible or rigid diagnostic urethroscopy.

Extracorporeal shockwave lithotripsy

For patients with bacteriuria or deemed at high risk of complications one RCT comparing the use of ofloxacin

or trimethoprim-sulphamethoxazole for three days prior and four days subsequent to ESWL in 56 patients with ureteric stents was identified [57]. They found no difference in rate of clinical UTI at seven days (no events) and no difference in post-ESWL bacteriuria. No reduction in fever at up to one week post-procedure using a single dose of levofloxacin 500 mg and no difference in the rate of bacteriuria [58].

Ureteroscopy

Lo *et al.*, included four RCTs with a total of 386 patients and found no evidence of benefit in reducing rate of clinical UTI [59]. The rate of bacteriuria was reduced using antibiotic prophylaxis. Panel discussion considered that despite low quality evidence suggesting no benefit in reducing risk of clinical UTI, clinicians and patients would prefer to use prophylaxis to prevent kidney infection or sepsis. Ideally this should be examined in a robustly designed clinical study.

PCNL

Tuzel *et al.*, investigated single dose ceftriaxone versus ceftriaxone plus a third-generation cephalosporin until after nephrostomy catheter withdrawal at mean (SD) of 3 (1) days in 73 participants undergoing PNL. They found no difference in rate of infectious complications between the two antibiotic regimens [61].

Two RCTs with overall low risk of bias comparing different antibiotic regimes in PNL were identified [60,61]. Seyrek *et al.*, compared the rate of SIRS following PNL in 191 patients receiving either a combination of sulbactam/ampicillin or cefuroxime. There was no difference in SIRS or urosepsis rates [60].

These two studies give moderate evidence that a single dose of a suitable agent was adequate for prophylaxis against clinical infection after PNL.

Transurethral resection of prostate

9 RCTs reviewed by Dahm *et al.*, six trials involving 1,666 men addressed the risk of septic episodes, 17 trials reported procedure related fever and 39 investigated bacteriuria. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction. Use of prophylactic antibiotics compared to placebo showed a relative risk reduction (95% CI) for septic episode and bacteriuria [62].

Transurethral resection bladder tumour

A literature search to February 2017 found one systematic review [330] which included two trials with

a total of 152 participants. No more recent RCTs were identified. The two reviewed trials found no difference in rate of bacteriuria and either had no clinical UTI events, or did not report clinical UTI[63].

Prostate biopsy

The meta-analysis on eleven studies with 1,753 patients showed significantly reduced infections after biopsy when using antimicrobial prophylaxis as compared to placebo/control [RR (95% CIs) = 0.56 (0.40 to 0.77)] [64-66]. Thus, antimicrobial prophylaxis is strongly recommended. However, the choice of regimens and duration of prophylaxis remains debatable.

Researchers are beginning to uncover the molecular details that underlie UTIs. Specifically, new diagnostic and therapeutic approaches based on the combination of host genetic factors, innate immunity, and bacterial virulence factors are needed to identify the patients most prone to UTIs to avoid the cost and potential side-effects of treatment[67].

Fortunately, advances being made in both basic and clinical scientific research of the urinary tract in patients and animal models are providing some explanations and insight into the clinical problems that remain with the management of UTIs.

Improved knowledge of the genetics, uropathogen virulence factors, and host immune responses to UTIs will enhance the ability of clinicians to more readily distinguish high-risk patients from uncomplicated patients, which is necessary to prevent major sequelae in these high-risk patients[67].

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