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Clinical Options for the Treatment of Urinary Tract Infections in Children

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ABSTRACT: Urinary Tract Infections (UTI) are a common cause of childhood febrile illness with 7% of girls and 2% of boys having a symptomatic culture positive UTI by the age of six years. Although there are conflicting views on the long term sequelae of UTI, as well as the place of prophylaxis, the universal aims of treatment of childhood UTI remain those of symptom alleviation, prevention of systemic infection and short and longer term complications. There is good evidence of historical and emerging resistance patterns, therefore rationalisation of prescription patterns by knowledge of sensitivities coupled with re-examination of empirical antibiotic choices is clearly important. Local formularies should reflect geographical resistance patterns along with best evidence on the duration and choice of antibiotic in order to maximize therapeutic effect, while minimizing the development of resistant strains.

KEYWORDS: urinary tract infection, pediatrics, therapeutics, antimicrobial

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Introduction

A urinary tract infection (UTI) is defined as the combination of significant growth of bacteria in the urine together with accompanying symptoms.[1] UTIs are a common childhood infection and a common cause of febrile illness with 7% of girls and 2% of boys having a symptomatic culture positive UTI by the age of six years.[2] A prevalence of 3–7% in children younger than two years presenting to emergency departments (ED) with a pyrexial illness has been reported.[3,4] Infection of the urinary tract occurs more frequently in boys than in girls below the age of one year; however, after the age of one year, UTI is more common in girls.[5] Following a UTI, a large number of children recover promptly and have no long-term complications; however, infections affecting the upper urinary tract are thought to cause irreversible damage to the renal parenchyma, which is evident as renal scarring. After a single UTI, 15–41% of children are thought to develop scarring[6–8] with long-term complications of renal scarring believed to include chronic kidney disease, proteinuria, hypertension, and complications in pregnancy.[9] There is some controversy regarding the relationship and frequency of renal scarring, with recent reviews questioning the basis of the traditionally assumed relationship between childhood UTI and renal dysfunction in later life.[10–12] In any event, it follows that prompt diagnosis and treatment of UTI is desirable as it is recognized that the risk of ascending UTI is significant.[13] It is plausible that renal scarring and subsequent renal impairment is related to age at the time of UTI. This is highest in infancy and declines significantly with age, with relatively low risk in children older than three years, and highest risk in children younger than two years.[7,14,15] Clearly, while the evidence for long-term sequel may be debatable, early initiation of appropriate treatment should minimize the likelihood of ascending UTI, scarring, and potentially prevent development of long-term complications.

A review of the patterns of antibiotic prescribing in the United States found that 70% of ambulatory visits for pediatric UTI were given antibiotics, with broad-spectrum antibiotics prescribed in one-third of cases. Children younger than two years, female sex, and pyrexia ≥38 °C were independent predictors of broad-spectrum antibiotic prescribing. The authors

noted a doubling in the use of third-generation cephalosporins and recommend that more judicious antibiotic use should be promoted.[16] This review considers the common pharmacological agents used for pediatric UTI to rationalize the goals of achieving symptom alleviation, bacterial clearance, and minimizing scarring, with reducing drug resistance and adverse affects from the use of antibiotics in children diagnosed with a UTI.

Pharmacological Agents

The choice of antimicrobial agent used empirically for the treatment of pediatric UTI is dictated by practical as well as clinical considerations. Importantly, geographic variations in bacterial susceptibility and resistance patterns to specific antibiotics should be borne in mind when choosing the agent to use before culture and sensitivity results being available. In addition, prior recent antibacterial use can affect resistance.[17] Table 1 summarizes the common drugs and doses used in the treatment of childhood UTIs.

Penicillins (ampicillin). Ampicillin is a beta-lactam antibiotic that can be given orally or intravenously. Its mode of action is similar to benzylpenicillin, but its amino group side-chain enables it to penetrate the outer membrane of some gram-negative bacteria accounting for its broader spectrum of activity. Ampicillin binds to penicillin-binding proteins in the bacterial cell wall and inhibits cell-wall synthesis. It is bactericidal against gram-positive and some gram-negative organisms including *Escherichia coli*, Proteus species, and *Staphylococcus*, but ineffective against *Klebsiella* and penicillinase-producing organisms. It is rapidly absorbed orally but bioavailability is only 20–60%. Some of the drug is metabolized by the liver and rest is eliminated unchanged in the urine.

There is concern over bacterial resistance to ampicillin with increased resistance related to widespread use for other childhood infections.[18] This is demonstrated by increased resistance in children who had used amoxicillin within 30 days of their UTI.[19] Ampicillin is considered a safe drug and has a low side-effect profile. It is mainly contraindicated in children with a penicillin allergy.

Co-amoxiclav (amoxicillin—clavulanate). Co-amoxiclav is a combination of amoxicillin and clavulanic acid. Amoxicillin is a bactericidal penicillin that inhibits enzymes in the bacterial cell-wall pathways; however, it is susceptible to degradation by beta-lactamases produced by resistant bacteria. Clavulanic acid is a beta-lactamase inhibitor and inactivates some beta-lactamase enzymes thereby extending the spectrum of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect. In UTIs, it is used orally or intravenously to treat beta-lactamase producing coliforms. The drug is rapidly absorbed orally and is better taken before food. It is eliminated by the kidneys. Co-amoxiclav is contraindicated in children with a known penicillin allergy. Twice Daily Dosing is Now a Treatment Option with Doses of 45–60 mg/kg/day of the Amoxicillin component.

Cephalosporins. Cephalosporins are used orally (eg, cephalexin) and intravenously (eg, cefuroxime) to treat UTIs. They are broad-spectrum, bactericidal antibiotics that contain a beta-lactam ring and have a mode of action similar to that of the penicillins. They are effective against *Staphylococcus*, *Klebsiella*, and *E. coli* and are resistant to the action of most beta-lactamases. Extended-spectrum beta-lactamase (ESBL)-producing *E. coli* is an increasingly common antibiotic-resistant

Table 1. Common antibiotics and doses used in the treatment of UTIs.

ANTIBIOTIC	ROUTE	DOSE
Ampicillin	Oral	Neonate <7 days 30 mg/kg bd 7–21 days 30 mg/kg tds 21–28 days 30 mg/kg qds 1 month – 1 year 62.5 mg qds 1–5 years – 125 mg qds 5–12 years 250 mg qds 12–18 years 250–500 mg qds
	Intravenous	1 month – 18 years 25 mg/kg qds
Cephalexin (Cefalexin)	Oral	Neonate <7 days 25 mg/kg bd 7–21 days 25 mg/kg tds 21–28 days 25 mg/kg qds 1 month–1 year 125 mg bd 1–5 years 125–250 mg bd 6–12 years 250–500 mg bd >12 years 500 mg bd
Cefuroxime	Intravenous	Neonate <7 days 25 mg/kg bd 7–21 days 25 mg/kg tds 21–28 days 25 mg/kg qds 1 month–18 years 20 mg/kg tds
Cefotaxime		Neonate 50 mg/kg daily in 2–4 divided doses >1 month 150 mg/kg daily in 2–4 divided doses
Ciprofloxacin	Oral	10 mg/kg bd
	Intravenous	Neonate 6 mg/kg bd 1 month–18 years 6 mg/kg tds
Co-amoxiclav	Oral	Birth–1 year 0.25 ml/kg of the 125/31 suspension tds 1–6 years (13–21 kg) 5 ml of the 125/31 suspension tds 7–12 years (22–40 kg) 5 ml of the 250/62 suspension tds
	Intravenous	Birth–3 months 30 mg/kg every 12 hours 3 months–18 years 30 mg/kg (max 1.2 g) every 8 hours
Co-trimoxazole	Oral	6 weeks–6 months 120 mg bd 6 months–6 years 240 mg bd 6–12 years 480 mg bd 12–18 years 960 mg bd
Gentamicin	Intravenous	1 month–18 years Initially 7 mg/kg, then adjusted according to serum gentamicin concentration
Nitrofurantoin	Oral	Age >3 months 750 microgram/kg QDS 12–18 years 5–100 mg QDS
Trimethoprim	Oral	Birth–1 month Initially 3 mg/kg single dose followed by 2 mg/kg twice daily >1 month 4 mg/kg twice daily 12–18 years 200 mg twice daily

strain and makes infections caused by these organisms more difficult to treat. Most ESBL-producing *E. coli* are resistant to cephalosporins, penicillins, fluoroquinolones, and trimethoprim. This may be related to the increased use of third-generation cephalosporins, which has doubled in the United States between 1998 and 2007 to make up 25% of ambulatory prescriptions.[16] Hypersensitivity reactions are the main adverse effect, and there is up to 10% cross-reactivity in patients with an allergy to penicillin.

Fluoroquinolones (ciprofloxacin). Ciprofloxacin is a fluoroquinolone used to treat upper UTIs. It is bactericidal and works by inhibiting DNA-gyrase activity and interfering with DNA replication. Quinolones have broad activity against gram-positive and gram-negative aerobic organisms; however, anaerobes are generally resistant to ciprofloxacin. Ciprofloxacin is well absorbed orally, rapidly and widely distributed into body tissues, and mostly eliminated by the kidneys. In children, the use of ciprofloxacin should be restricted to prove that pyelonephritis is caused by *E. Coli*.

Aminoglycosides (gentamicin). Gentamicin is an aminoglycoside antibiotic and an initial intravenous option for children with an upper UTI. It is used intravenously, because oral absorption is negligible. It is bactericidal and works by binding to the bacterial ribosomes interfering with protein synthesis. It is effective against all aerobic gram-negative rods including *Pseudomonas* and *Proteus*, and is also effective against staphylococci. All anaerobic organisms are resistant. It is eliminated unchanged by glomerular filtration.

The dose of gentamicin is weight related and should be calculated on the child's ideal weight to avoid excessive dosage. It requires close monitoring, and peak and trough levels should be measured during treatment. The initial once daily dose is 5–7 mg/kg. Subsequent doses are adjusted according to serum gentamicin concentration. The two major adverse reactions of gentamicin are ototoxicity and nephrotoxicity. Damage to the sensory cells of the ear can lead to hearing loss, balance problems, and tinnitus. Gentamicin damages cells in the proximal tubule, which causes kidney injury because of acute tubular necrosis. Renal function should be measured regularly, and if there is renal impairment, the interval between doses should be increased or the dose should be decreased. It is contraindicated in children with myasthenia gravis.

Nitrofurantoin. Nitrofurantoin is an oral antibiotic used in the treatment and prevention of lower UTIs. Nitrofurantoin is bacteriostatic at low concentrations and bactericidal at higher concentrations. It works by interfering with bacterial metabolism and cell-wall synthesis. It is active against many organisms including *E. coli*, *Staphylococcus saprophyticus*, *Enterobacter*, and *Klebsiella* species. It is also useful in the treatment of infection caused by ESBL *E. coli*. Nitrofurantoin only achieves antibiotic concentration in the urine with low circulating blood levels and poor tissue penetration making it unsuitable for the treatment of upper UTIs. Nitrofurantoin is well absorbed but it should be taken with food, as this improves its bioavailability. It is metabolized by the liver and eliminated by the kidneys. It is a useful antibiotic choice in pregnancy apart from at term when it is contraindicated. Other contraindications are renal failure, and neonates and children with G6PD deficiency.

Trimethoprim and co-trimoxazole. Trimethoprim is a bacteriostatic antibiotic used in the first-line treatment and prophylaxis of uncomplicated UTIs. *E. coli*, *Proteus*, *Klebsiella*, and *Enterobacter* species are usually sensitive to trimethoprim. It is rapidly absorbed orally, primarily metabolized in the liver, and the remainder is eliminated unchanged by the kidneys.

Trimethoprim and sulfamethoxazole (co-trimoxazole) are commonly used in combination because of their synergistic effects. They are combined in a ratio of 1:5, and oral and intravenous preparations are available. Trimethoprim is a diaminopyrimidine, and sulfamethoxazole is a sulfonamide. Co-trimoxazole inhibits the synthesis of tetrahydrofolic acid, which is required for the synthesis of bacterial amino acids and nucleic acid with the two components of the drug inhibiting different steps in the folate synthesis pathway. It is bactericidal against a broad spectrum of gram-positive and gram-negative aerobic bacteria with activity against some anaerobes. Both components of the drug are well absorbed, and its bioavailability is 100%. Although its use has declined because of the incidence of severe allergic reactions, adverse events, and widespread bacterial resistance comparable to that seen with ampicillin, it is still used in up to 49% of ambulatory UTIs.[16] Trimethoprim on its own is particularly used in UK practice, with high levels of resistance correspondingly seen.[20]

Trimethoprim and co-trimoxazole are contraindicated in folic acid deficiency, severe liver disease, renal failure, pregnancy, neonates, G6PD deficiency, and acute hepatic porphyria.

Clinical Studies

The most common causative organisms for childhood UTI are commensals of the perineum or bowel. Typically, of gram-negative rods, *E. coli* is the most commonly isolated organism (75–90% of cases).[21] Some strains of *E. coli* have features that increase their virulence including the possession of an endotoxin and cell-wall antigens. Other common bacterial causes are *Klebsiella*, *Proteus*, *Enterobacter*, and *Psuedomonas*. *Proteus mirabilis* is more common in boys and is associated with urinary stones. Gram-positive pathogens such as *S. saprophyticus* are more common in sexually active adolescent girls and group B *Streptococcus* in neonates and infants. In addition, any organism that gains access to the urinary tract system may cause infection, including fungi and viruses. Fungal infections are less common and are usually seen in diabetic or immune-compromised patients or patients with a long-term urinary catheter. Most UTIs are caused by a single organism; the presence of two or more organisms usually suggests contamination.

Resistance of pathogens to different antibiotics varies significantly between geographical regions; however, the pattern of resistance seen with ampicillin and latterly trimethoprim—sulfamethoxazole and trimethoprim is largely universal.[21,22] In particular, other than the ESBL strains, *E. coli* does not seem to demonstrate much resistance at the moment against second- and third-generation cephalosporins, aminoglycosides, nitrofurantoin, or quinolones.[22]

Prior exposure to antibiotics for UTI has been shown to be associated with higher rates of resistance.[23] This concept has been recognized for over three decades with coliform resistance demonstrated in association with prior antibiotic prescription in children with UTIs.[24] Resistance to trimethoprim, in particular, which has been the mainstay of antibiotic treatment in uncomplicated childhood UTI in the United Kingdom has been on the rise with an increase from 23 to 34% resistance observed in urinary isolates between 2002 and 2008.[20] Similar levels of resistance to co-trimoxazole has been observed in the United States.[25]

Increased resistance is associated with antibiotic prescription within the preceding three months; however, other factors are clearly contributory, illustrated by the 20.3% *E. coli* resistance to trimethoprim observed in children who had never been prescribed the drug before.[17]

Safety

When prescribing for children with UTIs, clinicians must be familiar with the side effects, toxicity, and adverse drug reactions (ADRs) of the currently available drugs. An ADR is an unwanted or a harmful reaction experienced following the administration of a drug or combination of drugs, which is suspected to be related to the drug. Owing to ethical considerations, the evaluation of drugs in the pediatric population is more limited than in adults, and studies in children tend to include smaller numbers. ADR profiles in children may differ from those seen in adults and may not be predicted by studies in adults.

Some adverse effects of antimicrobial agents can be because of hypersensitivity reactions. These can be immediate anaphylaxis or delayed. Delayed hypersensitivity reactions can manifest themselves in a variety of ways, the most common being skin rashes. Hypersensitivity reactions are most commonly seen with penicillins, cephalosporins, and sulfonamides.

The safety of quinolones in children and growing adolescents has been a concern after they were noticed to cause arthropathy in weight-bearing joints in juvenile animals. Quinolones were also demonstrated to cause arthropathy in other animals and in-vitro human cell culture. A systematic review of 105 studies looked at the safety data of children prescribed ciprofloxacin.[26] In 37 studies, there were no adverse events reported, whereas 68 studies reported adverse events. There were 1,065 reported adverse events overall, of which the most frequent events were musculoskeletal events, abnormal liver function tests, nausea and vomiting, and change in white blood cell counts. There were 258 musculoskeletal events, of which arthralgia accounted for half of these. All cases of arthropathy were resolved or improved with active management. The review concluded that despite musculoskeletal events being common, they are also reversible. The US Food and Drug Administration (FDA) has also recommended that, despite ciprofloxacin being effective in clinical trials, it should not be the drug of first choice in children. This is also over concerns of the number of adverse events affecting joints and soft tissues. It is only recommended for use for the treatment of complicated UTIs and pyelonephritis because of *E. coli*. In 2008, the FDA added a black box warning regarding the use of ciprofloxacin and spontaneous tendon rupture. In 2011, another warning was added stating that fluoroquinolones including ciprofloxacin may cause worsening of myasthenia gravis.

Nitrofurantoin and trimethoprim have fewer side effects and are considered safer in children, making them an ideal choice for long-term prophylactic antibiotics. Adverse reactions to nitrofurantoin are limited to Gastrointestinal disturbance and rash. Adverse events of co-trimoxazole are almost all because of sulfamethoxazole.

Efficacy

Clearly, local hospital or regional microbiology guidelines indicating the likely pathogens, resistance patterns, and their sensitivities should form the basis of initial empirical therapy if this is available. Once the child's specific culture and sensitivity are available, the treatment should be fashioned in keeping with the laboratory data.

American and UK guidance recommend early treatment of pyelonephritis and intuitively emphasizes avoiding treatment delay to minimize the risk of renal damage.[1,27] There is some evidence that suggests that no difference in scarring is found in children treated for pyelonephritis in whom antibiotics were started less than 12 hours from onset of fever compared with those for whom antibiotics were started 5 days from onset of fever.[28] This supports the assertion that once acute renal involvement is established, subsequent renal scarring is independent of the timing of therapy. However, early treatment may reduce symptoms and disease progression as seen on parenchymal localization on acute-phase Dimercaptosuccinic acid scans and inflammatory markers.[29,30] For this reason, most experts still recommend prompt treatment of febrile UTI, but in the context that a few hours are unlikely to have a significant effect on outcomes.[31]

The route of treatment will depend on the child's ability to tolerate the medications, for example oral medication would be relatively difficult to administer to a vomiting child. In infants younger than three months, children who are immunocompromised, toxic with urosepsis or with complicated pyelonephritis, parenteral therapy should be instituted.[22] The intravenous route (as compared to the intramuscular route) is

usually employed as a first preference among pediatricians. Beyond these considerations, as long as adherence to the treatment regime is assured, there is little difference between the efficacies of the orally (cefixime, ceftibuten, and amoxicillin/clavulanic acid) and parenterally used agents.[32] In patients who have been started on parenteral treatment, once they are clinically improved (usually within two to four days), they should be changed to an appropriate (by that time) laboratory-guided oral alternative.

There is no evidence from pooled data of increased efficacy when comparing oral with parenteral or switch (intravenous or intramuscular followed by oral) administration of antibiotics. Similarly, switch versus parenteral treatment and single-dose parenteral followed by oral therapy or switch therapy are equivalent to oral-only application.[33]

The duration of treatment depends on the patient's response to therapy. For upper UTIs, a 10-day course is recommended.[1] Patients who were commenced on intravenous therapy may be switched to oral treatment once they are well enough and allowed to complete this treatment duration.

When managing lower UTIs, studies have failed to demonstrate any difference in either bacterial eradication on culture or developing resistance when short courses (2–4 days) of oral antibiotics are used rather than longer courses of up to 14 days.[34]

It is notable that most studies of antibiotic efficacy related to route of administration excluded children with anatomical urinary tract abnormalities and this should be borne in mind when clinically assessing place and route of therapy. Although the therapeutic and pharmacological profiles would be unchanged, similar efficacy would be expected in these children. Lack of early clinical improvement with standard treatment routes should prompt re-evaluation of the child and consideration of anatomical imaging or alternate regimens.

Place in Therapy

Infants especially those younger than three months and any toxic appearing child should be referred to an in-patient setting for appropriate assessment of generalized sepsis and urosepsis.[1] In these infants, systemic antibiotic therapy is usually implemented at the onset of treatment as the risk of concomitant bacteremia is about 10%.[35] In addition, anatomical abnormalities are more likely to be present in younger infants.[36]

Any antibiotic that attains good urinary concentration is suitable. Systemic therapy can be chosen from the range of second- or third-generation cephalosporins, aminoglycosides, or co-amoxiclav. Oral agents are similarly available with a wide range of choices including but not restricted to nitrofurantoin, amoxicillin, trimethoprim (or co-trimoxazole) and first-generation cephalosporins. Care must be taken to avoid agents that do not sustain good therapeutic systemic levels outside of the urinary tract (eg, nitrofurantoin) in instances where systemic involvement has been suspected. Antibiotic dosing regimens should be kept specific to the agent utilized. Table 2 outlines some suggested empiric antibiotic options.

Emerging resistance patterns, in particular to co-trimoxazole (or trimethoprim), penicillin, and ciprofloxacin, have led to a call for rationalization of empirical prescribing for UTI. There is a suggestion that nitrofurantoin or first-generation cephalosporins be considered as initial therapy as they exhibit the best resistance profile.[25,37]

Notably, there has been no difference in outcome between once daily or standard dosing regimens for the aminoglyco¬side antibiotics.[38] As a result, single parenteral daily dosing with aminoglycosides or ceftriaxone is considered safe and effective and has shown promising use in the ambulatory treatment of pyelonephritis.[39]

The use of prophylactic antibiotics has been questioned in those children with a first-time UTI for over a decade.[40,31] This strategy has shown some evidence of benefit to a category of patients who have recurrent lower UTIs. This infection rate lowering benefit does not consistently appear to extend to those groups of patients who it has been previously aimed at – patients with previous upper UTIs or those with vesicoureteric reflux of any grade.[42,43] The evidence is therefore inconclusive with some studies having shown little benefit while others having shown consistent but modest benefit among children with higher grades (III—V) of reflux.[44]

Most recent guidelines[1,24] recommend that routine prophylaxis is unnecessary after a first uncomplicated UTI, even in children with higher grade reflux. An Italian guideline however, recommends prophylaxis in children with greater than or equal to Grade III reflux and in children with recurrent febrile UTIs.[45] However, it should be noted that the included studies in their meta-analyses enrolled few children with Grade V vesicoureteral reflux and pooled data for both sexes. Studies subsequently have suggested that there may be some benefit in girls with higher grade (III—IV) reflux, which is not apparent in similar male cohorts.[46] However, many pediatric nephrologists continue to use prophylactic antibiotics among the group of patients who experience recurrent UTIs, and have

Table 2. Empiric antibiotics for childhood UTI.

AGE/CLINICAL CONDITION	ANTIBIOTIC	ROUTE AND DURATION OF TREATMENT
Less than 3 months OR Any age but toxic/unwell/unable to tolerate orally	Ampicillin AND Gentamicin OR Cefotaxime AND Ampicillin	Intravenous (until clinical improvement allows oral switch for a total of 10 days)
>3 months with upper UTI/pyelonephritis	Cephalosporin, trimethoprim (or co-trimoxazole) or co-amoxiclav	Oral 10 days
>3 months with cystitis/lower UTI	Nitrofurantoin, trimethoprim (or co-trimoxazole) cephalosporin or amoxicillin	Oral 3–4 days

higher grades of reflux or urinary tract abnormalities. The recent RIVUR study demonstrated a 50% reduction in recurrent UTI in children given trimethoprim-sulfamethoxazole prophylaxis compared with placebo. This effect was most pronounced in children with an initial febrile infection and those with baseline bladder or bowel dysfunction. Consistent with other studies and recommendations, children with higher grades of reflux (III-IV) were more likely to have symptomatic recurrences than those with lower grades (I-II).Only a limited number of children developed renal scarring overall, and this did not differ between children given prophylaxis or placebo.[47] The length of follow up was only 2 years however, so longer term sequelae remains unknown. Until more generalisable evidence is available which answers the question of which specific groups definately benefit from prophylaxis, expert opinion will continue to be variable.

Prophylactic antibiotics do encourage a level of microbial resistance that has an undefined limiting effect on the treatment of breakthrough infections. This is demonstrated by a significantly higher proportion of trimethoprim-sulfamethoxazole resistant *E. coli* (63%) reported by the RIVUR investigators in their prophylaxis group than in the placebo group (19%).[47] Intuitively, children who develop a breakthrough UTI while using prophylactic antibiotics treatment ought to be commenced on a different antibiotic that is being used in prophylaxis.

Conclusion

The aims of treatment of childhood UTI are alleviation of symptoms, prevention of systemic infection, and short- and long-term complications. In addition, rationalizing the use of antibiotics to prevent the emergence of more-resistant pathogens is of vital importance. Reasonable evidence on the causative organisms, route and duration of treatment, and the role of prophylaxis exist, and together these should allow decisions on appropriate treatment to be made in conjunction with clinical and practical considerations. Traditional empiric antibiotic preferences should be re-examined in light of the high-resistance patterns observed, and local formularies should be developed to maximize therapeutic effect, while minimizing development of resistant strains.

Author Contributions

Conceived the concept: SR. Analyzed the data: SR, VS, JS, AR. Wrote the first draft of the manuscript: SR, VS, JS, AR. Jointly developed the structure and arguments for the paper: SR, VS, JS, AR. Agree with the manuscript results and conclusions: SR, VS, JS, AR. Made critical revisions: SR, VS, JS, AR. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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