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MINIREVIEW

Antimicrobial Effects of Antipyretics

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ABSTRACT Antipyretics are some of the most commonly used drugs. Since they are often coadministered with antimicrobial therapy, it is important to understand the interactions between these two classes of drugs. Our review is the first to summarize the antimicrobial effects of antipyretic drugs and the underlying mechanisms involved. Antipyretics can inhibit virus replication, inhibit or promote bacterial or fungal growth, alter the expression of virulence factors, change the surface hydrophobicity of microbes, influence biofilm production, affect the motility, adherence, and metabolism of pathogens, interact with the transport and release of antibiotics by leukocytes, modify the susceptibility of bacteria to antibiotics, and induce or reduce the frequency of mutations leading to antimicrobial resistance. While antipyretics may compromise the efficacy of antimicrobial therapy, they can also be beneficial, for example, in the management of biofilm-associated infections, in reducing virulence factors, in therapy of resistant pathogens, and in inducing synergistic effects. In an era where it is becoming increasingly difficult to find new antimicrobial drugs, targeting virulence factors, enhancing the efficacy of antimicrobial therapy, and reducing resistance may be important strategies.

KEYWORDS NSAIDs, ibuprofen, acetaminophen, paracetamol, antibacterial, antimicrobial, efflux pumps

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Acetaminophen (paracetamol), acetylsalicylic acid (ASA; aspirin, which is rapidly degraded to salicylic acid [SAL] *in vivo*), and other nonsteroidal anti-inflammatory drugs (NSAIDs), such as diclofenac, flurbiprofen, ibuprofen, and indomethacin, are some of the most commonly used drugs. They have antipyretic, analgesic, and apart from acetaminophen, anti-inflammatory activities through the inhibition of prostaglandin synthesis. In addition to these activities, it has been known, but neglected, for over 20 years that antipyretic drugs also have direct and indirect antimicrobial effects (1).

In an era where it is becoming increasingly difficult to find new antimicrobial drugs, it is important to understand these antimicrobial effects and their potential clinical implications. This review summarizes the antimicrobial effects of antipyretic drugs and the underlying mechanisms involved.

DIRECT EFFECTS ON BACTERIA AND FUNGI

(i) Influence on growth and replication. Antipyretics can inhibit and promote the growth or replication of bacteria and fungi. At therapeutic plasma levels, SAL and ASA inhibit the growth of *Campylobacter pylori* (2), *Helicobacter pylori* (3–5), and *Klebsiella pneumoniae* (6), as well as *Epidermophyton floccosum* (7, 8), *Microsporum* spp. (7), and *Trichophyton* spp. (7, 8). Ibuprofen at therapeutic levels inhibits the growth of *Escherichia coli* (9) and, at low pH, also *Staphylococcus aureus*, *Microsporum* spp., and *Trichophyton* spp. (8). Diclofenac inhibits the growth of *E. coli* (10), and flurbiprofen inhibits *Trichophyton* spp. (7).

The MICs of antipyretic drugs from *in vitro* studies are summarized in Table 1. The inhibitory activity of SAL, ibuprofen, diclofenac, and flurbiprofen can occur at concentra-

TABLE 1 MICs of antipyretic drugs

Organism	MIC (mg/ml) (temp [°C], pH of test) (reference) of indicated drug[a]				
	Acetaminophen (0.01–0.02 [15])[b]	Salicylic acid (0.15–0.30 [11])[b]	Ibuprofen (0.01–0.05 [12])[b]	Diclofenac (0.001–0.002 [13])[b]	Flurbiprofen (0.009–0.01 [14])[b]
Acinetobacter baumannii		3.20 (35, NS)[c] (93)	3.20 (35, NS) (93)	1.60 (35, NS) (93)	
Aggregatibacter actinomycetemcomitans			0.25 (37, pH 8.9) (1)		0.25 (37, pH 8.9) (1)
Bacillus spp.	2.50 (35, NS) (82)		0.35 (37, pH 7) (84), 2.50 (35, NS) (82), 12.50 (35, pH 7.4) (19)	0.05 (37, NS) (89), 0.05 (37, NS) (92)	
Burkholderia cepacia		3.20 (35, NS)[c] (93)	>3.2 (35, NS) (93)	0.80 (35, NS) (93)	
Campylobacter pylori		**0.13** (37, NS)[c] (2)		0.06 (37, NS) (2)	
Eikenella corrodens			0.25 (37, pH 9) (1)		0.13 (37, pH 8.9) (1)
Enterobacter cloacae	5.00 (35, NS) (82)	3.20 (35, NS) (93)	5.00 (35, NS) (82), >3.20 (35, NS) (93)	1.60 (35, NS) (93)	
Escherichia coli	2.50 (35, NS) (82)	1.00 (37, NS)[c] (109), 1.60 (35, NS)[c] (93), 2.76 (37, NS) (52)	**0.02** (NS, NS) (9), 1.00 (37, pH 7.2) (17), 2.50 (35, NS) (82), 3.20 (35, NS) (93)	**0.002** (37, NS) (10), 0.05 (37, NS) (92), 0.05 (37, NS) (91), 0.05 (37, NS) (89), 1.60 (35, NS) (93)	
Fusobacterium nucleatum			0.13 (37, pH 8.9) (1)		0.25 (37, pH 8.9) (1)
Helicobacter pylori		**0.07** (37, pH 7.5)[c] (5), **0.10** (37, pH 7) (3), 4.00 (37, NS) (83)	0.13 (37, NS) (83)		
Klebsiella spp.		**0.05** (37, pH 7.5) (6), 3.20 (35, NS)[c] (93)	>3.20 (35, NS) (93)	0.20 (37, NS) (92), 0.20 (37, NS) (89), 1.60 (35, NS) (93)	
Micrococcus luteus			0.35 (37, pH 7) (84)		
Paracoccus yeei	1.25 (35, NS) (82)		1.25 (35, NS) (82)		
Proteus spp.		1.60 (35, NS)[c] (93)	1.60 (35, NS) (93)	0.20 (35, NS) (93)	
Pseudomonas aeruginosa		1.58 (37, NS)[c] (109), 3.20 (35, NS)[c] (93)	>3.20 (35, NS) (93)	0.05 (37, NS) (92), 0.80 (37, NS) (89), 1.60 (35, NS) (93)	
Salmonella enterica serovar Typhi	2.50 (35, NS) (82)		2.50 (35, NS) (82)		
Salmonella Typhimurium				0.05 (37, NS) (89), 0.05 (37, NS) (92)	
Shigella spp.				0.05 (37, NS) (89), 0.10 (37, NS) (92)	
Staphylococcus aureus	1.25 (35, NS) (82)	>0.16 (35, pH 5) (8)	**0.04** (35, pH 5) (8), 0.35 (37, pH 6) (84), 1.25 (35, NS) (82), 6.25 (35, pH 7.4) (19)	0.05 (37, NS) (89), 0.05 (37, NS) (91), 0.05 (37, NS) (92), 10.00 (NS, pH 7) (20)	
Staphylococcus epidermidis		0.69 (37, pH 7.4) (30)	0.35 (37, pH 7) (84)		
Staphylococcus saprophyticus			1.25 (37, pH 7.2) (17)		
Stenotrophomonas maltophilia	3.20 (35, NS) (93)	1.60 (35, NS)[c] (93)	1.60 (35, NS) (93)	0.80 (35, NS) (93)	
Vibrio cholerae				0.05 (37, NS) (89), 0.05 (37, NS) (92)	
Wolinella recta			0.13 (37, pH 8.9) (1)		0.25 (37, pH 8.9) (1)
Aspergillus brasiliensis			3.10 (35, pH 7.4) (19)		
Aspergillus niger		>0.51 (35, pH 5) (7)			0.26 (35, pH 5) (7)
Candida albicans		>0.26 (35, pH 5) (7), >0.28 (35, pH 5) (8), 1.00 (37, pH 7)[c] (34), 2.65 (37, NS)[c] (109)	0.14 (35, pH 5) (8), 0.50 (37, NS) (16), 1.00 (37, pH 7.2) (17), 2.00 (35, pH 7) (18), 3.10 (35, pH 7.4) (19)	0.05 (37, NS) (16), 10.00 (NS, pH 7) (20)	0.032 (35, pH 5) (7)
Candida glabrata			0.25 (37, NS) (16), 3.00 (35, pH 7) (18)	0.15 (37, pH 7.2) (16)	
Candida krusei			0.25 (37, NS) (16), 1.00 (35, pH 7) (18)	1.00 (37, pH 7.2) (16)	
Epidermophyton floccosum		**0.13** (35, pH 5) (7), **0.14** (35, pH 5) (8), 1.20 (28, NS)[c] (85)	0.02 (35, pH 5) (8)	0.28 (28, NS) (85)	0.016 (35, pH 5) (7)
Microsporum spp.		**0.14** (35, pH 5) (7)	**0.01** (35, pH 5) (8)		
Mucor spp.		>0.28 (35, pH 5) (8)	0.12 (35, pH 5) (8)		
Penicillium expansum		0.35 (25, pH <5) (110)			0.016 (35, pH 5) (7)
Trichophyton spp.		**0.12** (35, pH 5) (8), **0.13** (35, pH 5) (7), **0.14** (25, NS)[c] (111), 1.90 (28, NS)[c] (85)	**0.005** (35, pH 5) (8), 0.20 (28, NS) (94)	0.70 (28, NS) (85)	**0.008** (35, pH 5) (7)

[a]MIC at or below therapeutic plasma levels indicated in bold. NS, not specified.
[b]Values in parentheses after the drug name indicate range of therapeutic plasma levels (mg/ml) [reference].
[c]Acetylsalicylic acid was used.

tions that are achieved with normal therapeutic doses (11–14). In contrast, the usual therapeutic plasma levels of acetaminophen are lower than the concentration at which inhibition of bacterial growth has been shown (15).

Interestingly, while supratherapeutic concentrations of acetaminophen, ibuprofen and diclofenac inhibit the growth of fungi (16–20), one study showed that at therapeutic concentrations, these antipyretics increase the growth of *Candida* spp. (21).

(ii) Motility. SAL reduces the motility of *Burkholderia cepacia*, *E. coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, and *Pseudomonas aeruginosa* (Table 2) (22, 23). However, only in *E. coli* has this effect been shown to occur at therapeutic plasma levels (23). At slightly higher concentrations, SAL reduces flagellin production in *E. coli*, as well as flagellum production in *P. mirabilis* (22). Celecoxib, a nonselective COX-2 inhibitor, reduces flagellar motility in *H. pylori* (24).

(iii) Adherence. Ibuprofen at a very low concentration (0.002 mg/ml) significantly decreases the adhesion of *E. coli* to uroepithelial cells (Table 2). This results from reduced fimbria production, as well as changes in surface hydrophobicity influencing the interaction between bacterial and host cells (9, 25, 26). Ibuprofen also reduces the adherence of *E. coli* to silastic catheters (27). Ibuprofen and diclofenac (tested only above therapeutic plasma levels) inhibit the adherence of *Candida albicans*, *C. glabrata*, and C. *krusei* (16). Diclofenac has higher inhibitory activity against the adherence of *C. albicans* and C. *glabrata*, while ibuprofen has a greater inhibitory effect on the adherence of *C. krusei* (16).

SAL at therapeutic levels reduces fibronectin binding in *S. aureus* and the adherence of *E. coli* to silastic catheters (27, 28). At concentrations slightly above the usual therapeutic plasma level, SAL reduces the production of adhesin in *Staphylococcus epidermidis* and fimbria production in *E. coli* (25, 26, 29, 30). At higher concentrations, it also reduces hemagglutinin production in *E. coli* (26). SAL also prevents the adhesion of *P. aeruginosa* and *S. epidermidis* to human corneal epithelial cells and the adherence of *P. aeruginosa*, *Haemophilus influenzae*, *S. epidermidis*, and *Streptococcus pneumoniae* to contact lenses (31).

(iv) Biofilm production. SAL at therapeutic levels decreases biofilm production by *Candida* spp. (21, 32–34), *E. coli* (25, 26, 35, 36), *P. aeruginosa* (37–39), and *S. epidermidis* (Table 2) (30, 38, 40). Biofilm production by *Salmonella enterica* serovar Typhimurium was also reduced by SAL, but the concentrations tested were not specified (41). One study showed no effect of SAL on biofilm production by *E. coli* (37).

There are conflicting reports on the effects of NSAIDs on biofilm production in fungi. While one study reports that ibuprofen and acetaminophen at therapeutic levels enhance biofilm production in *C. albicans* by inducing the secretion of aspartyl-proteases (21), another study shows a reduction in biofilm production by *Candida* spp. after exposure to ibuprofen and diclofenac at levels above therapeutic concentrations (32). Ibuprofen and diclofenac have a disruptive effect on mature biofilms in *C. albicans*, C. *glabrata*, and C. *krusei* (16).

(v) Other virulence factors. NSAIDs alter the expression of many virulence factors (Table 2). In *E. coli*, SAL modulates the expression of more than 144 genes, and, in *P. aeruginosa*, it modulates the expression of more than 331 genes (37, 39, 42). In *K. pneumoniae*, SAL at very low concentrations reduces the production of the polysaccharide capsule by more than 50% (6, 43, 44). In *P. aeruginosa*, SAL and ASA decrease the production of hemolysin, elastase, protease, and pyocyanin by about 55%, but this was only shown at concentrations above the usual therapeutic levels (37, 39). In *S. aureus*, SAL reduces the production of α-hemolysin (29). In *S. epidermidis*, SAL reduces the production of teichoic acid, polysaccharide capsule, and type 1 antigen (30). In *H. pylori*, ASA and indomethacin reduce urease and vacuolating cytotoxin activities (5, 45). Ibuprofen, at low concentrations, reduces hemolysin production in *E. coli* (9).

(vi) Metabolism. SAL at a concentration above therapeutic plasma levels leads to the downregulation of gluconeogenesis and glycolysis in *S. aureus* (46) and to activation of sugar transport (sorbitol and mannose) in *E. coli* (Table 2) (46). Ibuprofen and

TABLE 2 Direct and indirect antimicrobial effects of antipyretic drugs[a]

	Organism(s) tested and effect(s) (reference[s]) of indicated drug(s)					
Effect	Acetaminophen	Concn (mg/ml)	Salicylic acid	Concn (mg/ml)	Other NSAIDs	Concn (mg/ml)
Motility			Reduction of motility of *Burkholderia cepacia* (22), *Escherichia coli* (22, 23), *Proteus mirabilis* (22), *Proteus vulgaris* (22), *Providencia rettgeri* (22), *Providencia stuartii*	0.69 (22), **0.18** (23)		
			Blocking of flagellin production by *Escherichia coli*	0.69 (22)		
			Reduction in flagella production by *Proteus mirabilis*	2.76 (22)		
			No effect on motility of *Pseudomonas aeruginosa*	0.69 (22)		
Adherence			Reduction of fimbriae production by *Escherichia coli*	0.35 (25)	Reduction of adhesion of *Escherichia coli* to uroepithelial cells due to reduced fimbriae production and changes in surface hydrophobicity (ibuprofen)	**0.002** (9)
			Reduction of hemagglutinin production by *Escherichia coli*	1.38 (26)	Reduction of adherence of *Escherichia coli* to silastic catheters (ibuprofen)	0.39 (27)
			Reduction of fibronectin binding in *Staphylococcus aureus*	**0.03** (29)	Reduction of adhesion of *Candida albicans*, *Candida glabrata* and *Candida krusei* (ibuprofen)	0.13 (16)
			Reduction of adhesin production by *Staphylococcus epidermidis*	0.69 (30)	Reduction of adherence of *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae* to contact lenses (diclofenac)	**>0.001** (31)
			Reduction of adherence of *Escherichia coli* to silastic catheters	**0.28** (27), **0.14** (28)		
			Reduction of adherence of *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus epidermidis*, and *Streptococcus pneumoniae* to contact lenses	**>0.01** (31)		
			Reduction of adhesion of *Pseudomonas aeruginosa* and *Staphylococcus epidermidis* to human corneal epithelial cells	**>0.01** (31)		
Biofilm production	Increase of biofilm production by *Candida* spp.	**0.015** (21)	Reduction of biofilm production by *Candida* spp.	**0.2**[b] (21), **0.14** (32), **0.06**[b] (33)	Increase of biofilm production by *Candida* spp. (ibuprofen)	**0.02** (21)
			Reduction of biofilm production by *Escherichia coli*	**0.01** (35)	Reduction of biofilm production by *Candida albicans* (ibuprofen)	NS (32)
			Reduction of biofilm production by *Pseudomonas aeruginosa*	6[b] (37), **0.01** (39), **0.14** (38)	Disruption of mature biofilms in *Candida albicans*, *Candida glabrata* and *Candida krusei* (ibuprofen)	NS (16)
			Reduction of biofilm production by *Salmonella enterica* serovar Typhimurium	NS (41)		
			Reduction of biofilm production by *Staphylococcus epidermidis*	0.69 (30, 40), **0.14** (38)		
Other virulence factors			Reduction of polysaccharide capsule production in *Klebsiella pneumonia*	**0.002** (6), **0.03** (43), 0.35 (44)	Reduction in hemolysin production in *Escherichia coli* (ibuprofen)	**0.004** (9)
			Reduction of toxin production (hemolysin, elastase, protease, and pyocyanin) in *Pseudomonas aeruginosa*	1[b] (37), 1.38 (39)	Decrease in urease activity in *Helicobacter pylori* (indomethacin)	0.1 (45)
			Reduction of membrane proteins and pathogenicity of *Pseudomonas aeruginosa*	4.1 (112)		
			Reduction of urease and vacuolating cytotoxin activity in *Helicobacter pylori*	0.69[b] (5)		

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TABLE 2 (Continued)

Effect	Organism(s) tested and effect(s) (reference[s]) of indicated drug(s)					
	Acetaminophen	Concn (mg/ml)	Salicylic acid	Concn (mg/ml)	Other NSAIDs	Concn (mg/ml)
			Reduction of α-hemolysin production binding in *Staphylococcus aureus*	**0.03** (29)		
			Reduction of teichoic acid, polysaccharide capsule and type 1 antigen production by *Staphylococcus epidermidis*	0.69 (30)		
Metabolism			Downregulation of gluconeogenesis and glycolysis in *Staphylococcus aureus*	0.69 (46)	Increase in expression of cytochrome P450 in *Bacillus megaterium* (ibuprofen/indomethacin)	NS (47, 113)
			Activation of sugar transport (sorbitol, mannose) in *Escherichia coli*	0.69 (46)	Metabolic alternation and damages of cytoplasmic membrane in *Candida* spp. (ibuprofen)	3 (18)
					Inhibition of transition from yeast to hyphae in *Candida* spp. (ibuprofen)	0.1 (16)
Interaction with immune system	Reduction in transport and release of azithromycin and moxifloxacin by PMNL	**0.005** (74)	Reduction in transport and release of azithromycin and moxifloxacin by PMNL	**0.005** (74)	Reduction in transport and release of azithromycin and moxifloxacin by PMNL (ibuprofen)	**0.005** (74)
			Reduction in uptake of azithromycin by PMNL	**0.005** (74)		
			Increase in phagocytosis of *Klebsiella pneumonia by* PMNL	**0.03** (43), 4 (86)		
Antibiotic susceptibility	Decrease in susceptibility of *Serratia marcescens* to cefotaxime, kanamycin	**0.005** (60)	Decrease in susceptibility of *Escherichia coli* to ofloxacin	**0.14** (93)	Increase in susceptibility of *Helicobacter pylori* to metronidazole and clarithromycin (indomethacin)	0.04 (45)
	Induction of β-lactamase activity in *Serratia marcescens*	**0.005** (60)	Increase in susceptibility of *Acinetobacter baumannii* to ceftriaxone, ciprofloxacin, gentamicin, imipenem	0.35 (65)	Decrease in susceptibility of *Bacillus pumilus*, *Escherichia coli*, *Salmonella* Typhimurium, *Shigella dysenteriae*, *Staphylococcus aureus and Vibrio cholerae* to streptomycin (diclofenac)	0.05 (92)
	Increase in susceptibility of *Candida* spp. to amphotericin B	NS (34)	Decrease in susceptibility of *Burkholderia cepacia* to chloramphenicol, ciprofloxacin, trimethoprim	1.38 (48)	Increase in susceptibility of *Candida* spp. to azoles and amphotericin B (18, 71, 72) (ibuprofen)	0.06 (18)
			Decrease in susceptibility of *Campylobacter jejuni* to chloramphenicol, ciprofloxacin, erythromycin, rifampin, tetracycline	**0.14** (49), **0.10** (50, 51)	Reversal of overexpression of efflux pumps in *Candida* spp. (ibuprofen)	100 (72)
			Decrease in susceptibility of *Escherichia coli* to ampicillin, cephalosporins, chloramphenicol, fluoroquinolones, nalidixic acid, tetracycline	**0.07** (55), **0.14** (52, 54), 0.69 (53, 87, 88)		
			Increase in susceptibility of *Escherichia coli* to aminoglycosides	**0.28** (55)		
			Increase in susceptibility of *Helicobacter pylori* to amoxicillin, clarithromycin, metronidazole	1.38 (3, 69)		
			Decrease in susceptibility of *Klebsiella pneumonia* to aztreonam, cefazolin, cefonicid, cefoperazone, ceftizoxime, clindamycin, doxycycline, mezlocillin, norfloxacin, trimethoprim-sulfamethoxazole	0.35 (44)		
			Increase in susceptibility of *Klebsiella pneumonia* amikacin, gentamicin, tobramycin	0.35 (44, 68)		
			Decrease in susceptibility of *Pseudomonas aeruginosa* to biapenem, carbenicillin, cefozopran, cefpirome, chloramphenicol, ciprofloxacin, gentamicin, imipenem, moxalactam, meropenem, norfloxacin, ofloxacin, panipenem, piperacillin	**0.14** (39), 0.55 (56), 4.4 (57)		

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TABLE 2 (Continued)

Effect	Organism(s) tested and effect(s) (reference[s]) of indicated drug(s)					
	Acetaminophen	Concn (mg/ml)	Salicylic acid	Concn (mg/ml)	Other NSAIDs	Concn (mg/ml)
			Increase in susceptibility of *Pseudomonas aeruginosa* to aztreonam, carbenicillin, cefotaxime, cefpiramide, chloramphenicol, piperacillin	0.55 (56)		
			Decrease in susceptibility of *Pseudomonas aeruginosa* to	4.1 (112)		
			Decrease in susceptibility of *Salmonella enterica* serovar Typhimurium to ampicillin, cefoperazone, chloramphenicol, ciprofloxacin, nalidixic acid, tetracycline	0.69 (58), 0.35 (59)		
			Decrease in susceptibility of *Serratia marcescens* to ampicillin, cefotaxime, cefoxitin, cephaloridine, ciprofloxacin, nalidixic acid, norfloxacin	**0.14** (60–62)		
			Increase in susceptibility of *Serratia marcescens* to cephalothin, kanamycin	0.41 (60)		
			Decrease in susceptibility of *Staphylococcus aureus* to ciprofloxacin, norfloxacin, fusidic acid	**0.28** (64), 0.69 (63)		
			Induction of β-lactamase activity in *Serratia marcescens*	**0.15** (60)		
			Increase in susceptibility of *Candida* spp. to azoles and amphotericin B	**0.03** (34)		
Mutations			Suppression in the ability of metronidazole to induce mutations to rifampin in *Helicobacter pylori*	**0.10**[b] (3)		
			Increase (70-fold) in frequency of mutations leading to fluoroquinolone resistance in *Campylobacter jejuni* under selection with ciprofloxacin	**0.10** (50)		
			Increase in mutations leading to fluoroquinolone resistance in *Staphylococcus aureus*	**0.28** (64, 73), 0.69 (63)		
Effects on viruses			Inhibition of hepatitis C virus cell entry (reduction in claudin-1 receptor)	0.55[b] (75)		
			Decrease in hepatitis C virus replication (modulation of inducible nitric oxide synthase and activation of p38 mitogen-activated protein kinase and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2)	0.55[b] (76, 77)		
			Decrease of influenza virus replication (inhibition of nuclear factor-kappa B)	**0.14**[b] (78)		
			Decrease of flavivirus replication (activation of p38 mitogen-activated protein kinase)	**0.14** (79)		

[a]Concentrations at or below therapeutic plasma levels are indicated in bold. NS, not specified. PMNL, polymorphonuclear leukocytes.
[b]Acetylsalicylic acid was used.

indomethacin induce cytochrome P450 (CYP) production in *Bacillus megaterium*, which renders the bacteria considerably more sensitive to oxidant insults (47). Ibuprofen at high concentrations induces metabolic alternation and also damages the cytoplasmic membrane in *Candida* spp. (18). It also inhibits the transition from yeast to hyphae and, therefore, germ tube formation in *Candida* spp. (16).

INDIRECT EFFECTS ON BACTERIA AND FUNGI

Interaction with antimicrobials. SAL increases the antimicrobial susceptibility of many pathogens. Less commonly, it leads to decreased susceptibility, mainly to aminoglycosides but also to β-lactams and fluoroquinolones (Table 2) (3, 39, 44, 48–68). When *H. pylori* is exposed to ASA and other COX inhibitors, its susceptibility to amoxicillin, clarithromycin, and metronidazole increases (3, 45, 69, 70). In *Serratia marcescens*, ASA, SAL, and acetaminophen at therapeutic plasma levels induce β-lactamase activity (60). Acetaminophen at low levels also decreases the susceptibility of *S. marcescens* to cefotaxime and kanamycin (60). In *Candida* spp., ibuprofen or ASA in combination with azoles and amphotericin B leads to synergistic effects (18, 34, 71, 72). The MICs of *Candida* spp. to fluconazole decrease up to 128-fold in the presence of ibuprofen (18). By reversing the overexpression of efflux pumps, ibuprofen can diminish *Candida* resistance (72).

The main mechanism underlying changes in susceptibility is a change in the permeability of the outer membrane porin protein (OMP) to antibiotics. This is mainly through decreases or increases of OMPs or efflux pumps.

Antipyretics may also alter susceptibility to antibiotics by inducing mutations in bacterial genes. SAL at therapeutic levels suppresses the ability of metronidazole to induce mutations to rifampin in *H. pylori* (3). In contrast, in *Campylobacter jejuni*, under pressure from ciprofloxacin, SAL increases the frequency of mutations, leading to as much as a 70-fold increase in fluoroquinolone resistance (50). SAL also increases mutations leading to fluoroquinolone resistance in *S. aureus* (63, 64, 73).

Acetaminophen, SAL, and ibuprofen at very low concentrations reduce the transport and release of azithromycin and moxifloxacin by polymorphonuclear leukocytes (PMNL) (Table 2) (74). SAL also reduces the uptake of azithromycin by PMNL (74).

EFFECTS ON VIRUSES

ASA/SAL inhibit the cell entry and replication of hepatitis C virus (75–77), as well as the replication of flavivirus and influenza virus (78, 79). The inhibition of replication mostly occurs at therapeutic levels (78, 79). One of the underlying mechanisms is inhibition of the transcription factor nuclear factor-kappa B, which is critical for the inducible expression of multiple cellular and viral genes involved in inflammation, including interleukin-1 (IL-1), IL-6, and adhesion molecules (78, 80). Another mechanism is the activation of p38 mitogen-activated protein kinase and mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 (76, 77, 79).

DISCUSSION

As antipyretics are commonly coadministered with antimicrobial therapy, it is important to understand the interactions between these two classes of drugs. Antipyretics primarily act by inhibiting prostaglandin synthesis. Fungi (unlike bacteria and viruses) produce prostaglandins, and although their exact function is uncertain, it is thought that they influence virulence, in particular controlling the yeast-to-hypha transition and biofilm production (32, 34, 81). Aside from prostaglandin inhibition, as detailed in this review, other mechanisms by which antipyretic drugs influence pathogens include inhibiting virus replication (75–79), inhibiting or promoting bacterial and fungal growth (1–3, 5–9, 16–21, 34, 45, 52, 82–85), altering the expression of virulence factors (5, 6, 9, 29, 30, 37, 39, 43–45), changing the surface hydrophobicity of microbes (9), influencing biofilm production (16, 21, 30, 32, 33, 35, 37–41), affecting motility (22, 23), adherence (9, 16, 25–31), and metabolism (16, 18, 46), interacting with the transport and release of antibiotics by PMNL (43, 74, 86), modifying the susceptibility of microbes to antimicrobial therapy (3, 18, 34, 39, 44, 45, 48–65, 68, 69, 72, 87, 88), and inducing or reducing the frequency of mutations leading to antimicrobial resistance (3, 50, 63, 64, 73).

SAL mostly inhibits the growth of Gram-negative bacteria and fungi, while ibuprofen and diclofenac also inhibit the growth of Gram-positive bacteria, though this may simply reflect the particular bacteria that were chosen for testing in different studies (2, 3, 5–8, 51, 52, 60, 84, 89–92). In considering the clinical relevance of the antimicrobial effects of antipyretics, it is important to understand that the reported MICs of antipyretic drugs vary, sometimes considerably, according to the culture medium, incubation temperature, and pH used. Inhibition of growth is greater at pHs lower than 7 (7, 8, 19, 84). The use of different temperatures and pH conditions in the studies summarized in Table 1 limits comparison. In addition, the antipyretic concentrations also vary between studies, and it is possible that lower concentrations, had they been tested, might also inhibit growth. While some studies use ASA for the determination of MICs, others use SAL, which is the active *in vivo* metabolite of ASA. One study, which compared the MICs of the two forms, showed a twofold difference, suggesting that results obtained using these drugs are not directly comparable (60). Since ASA is rapidly degraded to SAL *in vivo*, the data for SAL was used whenever possible in this review. Interestingly, a recent study showed that NSAIDs are substrates of efflux pumps in Gram-negative bacteria. When the pumps are inhibited by an additional drug, the MICs to NSAIDs decrease significantly (93). This combination therapy, as well as changes in the structure of antipyretics, might increase the antimicrobial activities of antipyretics. Further studies are necessary to determine the full range of MICs of antipyretic drugs.

Although many of the MICs for antipyretic drugs are above the therapeutic plasma levels normally attained, higher drug concentrations might be reached in urine, synovia, or with topical therapy. Antipyretic drugs in those situations might reach levels where they inhibit microbial growth or influence microbes by some of the other mechanisms described. Topical ibuprofen, for example, is more effective in suppressing the growth of *Trichophyton* than topical clotrimazole (94). Another example is that two thirds of women with uncomplicated urinary tract infections (80% with *E. coli*) treated with ibuprofen recover without antibiotics (95). Although this finding is considered to result from the anti-inflammatory effects of ibuprofen, it might also be attributable to the antimicrobial effects of ibuprofen, which include blocking of adherence to uroepithelial cells, reduced motility, and reduced toxin and biofilm production, as well as inhibition of growth (9, 25, 26). Diclofenac and other NSAIDs inhibit bacterial DNA synthesis (10, 91) in *E. coli*; this was shown to be through the inhibition of a DNA polymerase (96).

Of further particular relevance for clinical practice is the effect of NSAIDs on the antibiotic susceptibility of pathogens. Changes in susceptibility mostly result from a change in direct antimicrobial penetration through cell membranes of bacteria or from an increase or decrease in efflux through the membranes (3, 39, 44, 48–68). However, decreased susceptibility can also result from induced β-lactamase activity (60). By understanding these mechanisms, these synergistic effects can be exploited in the treatment of infectious diseases and potential compromising effects on antimicrobial efficacy can be avoided. Notably, SAL at therapeutic levels can increase or decrease the frequency of resistance mutations in bacteria under antibiotic pressure, and ibuprofen reverses overexpression of efflux pumps and can therefore reverse resistance in *Candida* spp. (3, 50, 63, 64, 72, 73). Furthermore, ibuprofen also increases the susceptibility of *Candida* spp. to azoles or amphotericin B. Both mechanisms are promising for treatment of resistant fungal infections (18, 34, 71, 72). Several NSAIDs are metabolized through CYP enzymes. CYPs have also been identified in bacteria, with the highest number in mycobacteria (97). The one study reporting the effect of antipyretics on bacterial CYPs found that an induction of CYPs renders bacteria more sensitive to oxidant insults (47).

More evidence for the potential antimicrobial effect of antipyretics can be drawn from animal studies. In mice, ASA and ibuprofen enhance the effect of pyrazinamide during the initial phase of tuberculosis treatment and diclofenac protects mice from dying from *Salmonella* infection (89, 98). In cows, higher peak levels of ceftizoxime can

be detected in plasma after coadministration with acetaminophen (99). In rabbits with *S. aureus* endocarditis, ASA reduces vegetation bacterial density, hematogenous bacterial dissemination, and the frequency of embolic events (100). While treatment with NSAIDs improves survival in sepsis in animal models (101–103), this was not the case in one study in humans (104).

It is difficult to discern which of the effects outlined in this paper are the most clinically relevant. Good evidence exists for SAL-induced induction of phenotypic resistance in Gram-negative bacteria through permeability changes of the outer membrane (downregulation of OMPs, upregulation of efflux pumps, and increase in membrane potential) (36, 48, 50, 53, 56–58, 60, 87, 88, 105–107). However, it is unclear whether these effects, observed *in vitro*, compromise the efficacy of antimicrobial therapy *in vivo* or if they can be used beneficially. There is also the possibility of SAL leading to the selection of resistant bacteria by these mechanisms. Further studies are necessary to determine whether concurrent use of SAL necessitates a change in antibiotic dose.

Good evidence also exists for the reduction of biofilm formation and bacterial adherence by SAL in *Candida* spp., *E. coli*, *Salmonella*, *S. aureus*, *S. epidermidis*, and *P. aeruginosa* (21, 25–33, 35, 37–41) and by ibuprofen in *Candida* spp. and *E. coli* (9, 16, 28). This could be helpful in the treatment of infections in the presence of foreign material, especially intravenous or urine catheters.

Interpretation of the findings of the studies identified in this systematic review is limited by the heterogeneity of the studies, including the wide variation in the concentrations of antipyretics used, the particular pathogens and microbial factors chosen to test, and the culture conditions used in the different studies. The potential detrimental effects of antipyretics on the immune response to infection have been discussed previously (108). Our review highlights that antipyretic drugs also influence the response to antimicrobial therapy. In general, NSAIDs have broad-spectrum antimicrobial activity, although apart from SAL/ASA, inhibition of pathogen growth mostly occurs at levels above therapeutic plasma concentrations. However, antipyretics also have potent activity in reducing adherence, biofilm production, and other virulence factors, as well as the ability to both increase and decrease antibiotic susceptibility. Targeting virulence factors and reducing resistance provides a novel strategy to enhance antimicrobial therapy. Antipyretics could be useful in the management of biofilm-associated infections, as adjuvant therapy in viral, bacterial, and fungal infections, or in reducing antimicrobial resistance. Changes in the structure of antipyretics might increase their antimicrobial activities, and further research might lead to potent antimicrobial agents.

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